RISK MANAGEMENT PLAN (RMP)

Active substance(s) (INN or common name):	Ulipristal acetate
Pharmaco-therapeutic group **(ATC Code):**	Sex hormones and modulators of the genital system, emergency contraceptives G03AD02
Name of Marketing Authorisation Holder or Applicant:	Laboratoire HRA Pharma
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	ellaOne

Data lock point for this RMP	14 May 2014	Version number	13
Date of final sign off	09 January 2015		

TABLE OF CONTENTS

List of Tables

PART I PRODUCT(S) OVERVIEW

The new modular structure is applicable from version 12 only.

Part	Module/annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted/ or Not Applicable
Part II Safety Specification	SI Epidemiology of the indication and target population(s)	01/02/2013	V 13
	SII Non-clinical part of the safety specification	20/08/2014	V 13
	SIII Clinical trial exposure	31/01/2013	V 12
	SIV Populations not studied in clinical trials	20/08/2014	V 13
	SV Post authorisation experience Only required for updates to the RMP	20/08/2014	V 13
	SVI Additional EU requirements for the safety specification	20/08/2014	V 13
	SVII Identified and potential risks	20/08/2014	V 13
	SVIII Summary of the safety concerns	20/08/2014	V 13
Part III Pharmacovigilance Plan		20/08/2014	V 13
Part IV Plan for post-authorisation efficacy studies		31/01/2013	V 12
Part V Risk Minimisation Measures		09/01/2015	V 13
Part VI Summary of RMP		09/01/2015	V 13
Part VII Annexes	ANNEX 2 Current or proposed SPC/PIL	09/01/2015	V 13
	ANNEX 3 Worldwide marketing status by country	20/08/2014	V 13
	ANNEX 4 Synopsis of clinical trial programme	20/08/2014	V 13
	ANNEX 5 Synopsis of pharmacoepidemiological study programme	31/01/2013	V 12

Part	Module/annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted/ or Not Applicable
	ANNEX 6 Protocols for proposed and on-going studies in Part III	31/08/2013	V 13
	ANNEX 7 Specific adverse event follow-up forms	31/01/2013	V 12
	ANNEX 8 Protocols for studies in Part IV	01/02/2013	V 13
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	31/08/2013	V 13
	ANNEX 10 Details of proposed additional risk minimisation activities	31/08/2013	V 13
	ANNEX 11 Mock up examples	31/01/2013	V 12
	ANNEX 12 Other supporting data	01/02/2013	V 13

QPPV name Dr. Jean-Louis Abitbol

QPPV signature [redacted]

Contact person for this RMP

Name: [redacted]

Position: [redacted]

E-mail: [redacted]

Overview of versions:

Version number of last agreed RMP:

Version number	12 (July 2013)
Agreed within	PRAC Assessment Report 18/07/2013 on EMEA/H/C/001027/MEA 006.6 – CHMP opinion 25/07/2013

Current RMP version under evaluation:

RMP Version number	Submitted on	Submitted within
14	25 July 2014	PSUR 8

Invented name(s) in the European Economic Area (EEA)	ellaOne
Authorisation procedure	Centralised (EU/1/09/522/001)
Brief description of the product including: • chemical class • summary of mode of action • important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines	Ulipristal acetate is an orally-active synthetic selective progesterone receptor modulator characterized by a tissue-specific mixed agonist/antagonist progesterone effect. Ulipristal acetate acts via high-affinity binding to the human progesterone receptor. The primary mechanism of action is inhibition or delay of ovulation. Pharmacodynamic data show that even when taken immediately before ovulation is scheduled to occur, ulipristal acetate is able to postpone follicular rupture in some women. Ulipristal acetate binds in vitro to the human progesterone, glucocorticoid and androgen receptors at 6, 1.5 and 0.2 times the affinity of the endogenous ligand. In vivo, it exerts a tissue-specific mixed agonist/antagonist progestin activity and to a lesser extent anti-glucocorticoid and anti-androgen activity (at doses approximately 50-fold greater than those needed for antiprogestin effect).
Indication(s) in the EEA Current (if applicable)	Emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.
Proposed (if applicable)	Not applicable.
Posology and route of administration in the EEA Current (if applicable)	30 mg single intake
Proposed (if applicable)	Not applicable.
Pharmaceutical form(s) and strengths Current (if applicable)	Tablet 30 mg
Proposed (if applicable)	Not applicable.

Country and date of first authorisation worldwide	European Union 15 May 2009
Country and date of first launch worldwide	FR, UK, DE, BE 01 October 2009
Country and date of first authorisation in the EEA	European Union 15 May 2009

Is the product the subject of additional monitoring in the EU? Yes ☐ No ☒

PART II MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

Indication: Emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.

Brand names of concerned products (with this indication): ellaOne.

1.1 Epidemiology of the disease

Indication	Emergency contraception (EC) is defined as the use of a drug or device as an emergency measure to prevent pregnancy after unprotected sexual intercourse (UPI) (Cheng 2008). Unprotected intercourse is defined as failure of a contraceptive method, or an intercourse which takes place in the absence of contraception in a woman who is fertile, not pregnant and not intending to be pregnant. EC methods include emergency contraceptive pills and intra-uterine device (IUD). The IUD requires an experienced clinician and medical infrastructure for insertion and is not women preferred choice. Oral EC is most often preferred method and two dedicated hormonal emergency contraceptives are registered in the EU: • a single tablet of 1.5 mg levonorgestrel (LNG) approved within 72 hours of UPI, • a single tablet of 30 mg ulipristal acetate (UPA) (ellaOne), approved within 120 hours (5 days) of unprotected intercourse or contraceptive failure.
Target population	Women of reproductive age.
Incidence of target indication	Estimations of the number of unprotected intercourses in the EU: In a recent survey on the use of EC in 5 European countries amongst women in the reproductive age (n=7,170) and irrespective of regular method of contraception, pregnancy status or intention to get pregnant, 30% of all women claim to have had at least one course of UPI over the last year (BVA Healthcare 2012 – HRA2914-557). Given the number of 77 656,000 women in fertile age in the EU, the estimated number of women with at least one course of UPI per year in the EU would be over 23 million. A conservative assumption is to admit that each of these women has a maximum of one UPI each year and that all other intercourses are well protected by the various contraceptive methods. Estimating the total number of intercourses per year in the EU is difficult, but taking a conservative assumption of an average frequency of once per woman per 2 weeks, the total number of intercourses per year in the EU would result in over 2 billion intercourses (26×77 656,000). An average frequency of once per 4 weeks would result in over 1 billion intercouses (13×77 656,000). Depending on the assumption, the proportion of UPI would be at least 1.2% or 2.4% of the total number of intercourses.
Prevalence of target indication	Estimations of the number of uses of EC: If we estimate that 6 million boxes of EC have been sold in the EU in 2012, then the % use of EC for UPI is maximally 6/23×100 = 26%. This number is in line with the percentage of EC use in the survey in 5 European countries, which

	was 24% of the women who had had at least one UPI over the last year. EC use can also be estimated based on data from representative samples of women of reproductive age collected via either cohort studies on contraceptive use or repeated cross-sectional surveys that include questions on lifetime or annual emergency contraception use. Three studies have been conducted in Europe: a cohort study in France (Goulard 2006), and two cross-sectional surveys, one in France (Moreau 2006) and one in the UK (Marston 2005). The COCON cohort (Goulard 2006) is a nationally-representative sample of French women 18-44 years old followed-up every year for four years from 2000. Data from the 2001 follow-up indicate that 3.6% of women in the sample reported have used emergency contraception during the first year of follow-up, of whom 41% had used it previously. The annual EC incidence rate based on the data from this study is estimated to be 2.1%. A 2004 cross-sectional survey of 7,490 French women aged 15-44 years revealed lifetime use of emergency contraception of 16.9% among women who have had sexual intercourse (Moreau 2006). The lifetime use increased 7.1% from the same survey conducted in 1999. An increase in lifetime use of 7.1% over a 5-year period suggests an annual incidence of 1.4%. Significantly greater lifetime use was reported by women in the youngest age groups (30.7% and 31.8% in women 18-19 and 20-24, respectively) than in the oldest age groups (10.8% and 8.7% in women 35-39 and 40-44, respectively), with the greatest increase over the 5-year period between the two surveys occurring in women 18-19 (20.3% increase). The upper limit of the annual incidence rate can be therefore estimated at 4.1%. In a 2008/09 UK cross-sectional survey, 7% of British women aged 16-49 reported having used emergency contraception in the past year and most had done so only once, a figure consistent with the data reported for the last decade (from 5% in 2007-08 to 8% in 2000/01) (Office for National Statistics 2009). If all the women reporting emergency contraception use were new users, then the maximum annual incidence rate would be 7%; the true incidence rate is likely lower, given that around 1% of the women surveyed reported having used it more than once in the course of the previous year. The incidence rates in the UK and France appear to be similar. Additional cross-sectional studies in more limited samples conducted in other European countries suggest small inter-country variation in incidence even though data often come from the younger population which is therefore not representative of the entire target population. In a cross-sectional survey of 1,154 Polish university students, 14% reported lifetime use of emergency contraception (Olszewski 2007). In a Finnish survey (Falah-Hassani 2007) involving a population-based sample of some 4,000 12-18-year-old female adolescents in 1999, 2001 and 2003, 9% of the overall sample reported lifetime use of emergency contraception, with a maximum of 29% reported by 18-year-olds in 2003. Altogether, these surveys indicate that the annual use (incidence) rate of EC is approximately 5% of women of reproductive age
Mortality in target indication	None.
Potential health risk	No potential health risks are associated with emergency contraception use. However, in the event of emergency contraception failure, pregnancy may

	result. The epidemiology of the two main potential pregnancy-associated risks (ectopic pregnancy and congenital anomalies) is reviewed below.
Demographic profile of target population	All sexually-active women of reproductive age are potential users of EC. The mean age of first sexual intercourse is between 16 and 18 years in the majority of European countries (Fontes 2006). In all studies, the main reasons for emergency contraception use were intercourse without contraception, condom failure, or missed oral contraceptive doses. The main reason for not using emergency contraception is that women underestimate the risk of conception. For example in the European Survey 41% of women believes that sex outside of the midcycle week is safe, 51% believe that coitus interruptus is an effective method (BVA Healthcare 2012 – HRA2914-557).

1.2 Concomitant medication(s) in the target population

There is no identifiable pattern regarding concomitant medications in the target population.

The target population of women of reproductive age is a young and healthy population using mainly non-prescription drugs or treatment usually administered for common diseases such as upper respiratory infections, allergies, vaginal fungal infections, gastric acid reflux.

In the phase 3 trials, the most commonly used concomitant medications were analgesics (about 20%) and anti-inflammatory products (17%). Concomitant medications used in at least 3% of the study population otherwise included antibiotics (3-4%), sex hormone medications (levonorgestrel or Yuzpe EC, regular contraception, 2-3%), antihistamines drugs (2-3%), common cold treatment (2-3%).

In a survey (FUM-008, HRA2914-544), where a total of 1233 ellaOne cases were collected, from 315 HCPs in 6 European countries, concomitant drugs having potential interactions with ellaOne were used by 2.6% of patients.

1.3 Important co-morbidities found in the target population

No significant co-morbid conditions have been identified in the target population of women of reproductive age.

PART II MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings (from non clinical studies)	Relevance to human usage
• **Single-dose study** Single dose toxicity studies were conducted in rats and rabbits and showed the lethal dose of ulipristal acetate to be 1250 mg/kg in rats and >1250 mg/kg in rabbits	These observations are of no relevance to humans.
• **Repeat-dose study** **Pituitary, adrenal, ovary and mammary glands, uterus**: Repeated dose toxicity studies conducted in rats and monkeys have shown a dose-related disruption of the hypothalamic-pituitary-adrenal axis, resulting from anti-progesterone and anti-glucocorticoid activities. Key findings observed at mid and high dose levels, in various organs are related to increases in serum prolactin and corticosterone levels: - Increased weight of pituitary in rats and monkeys and pituitary hyperplasia in rats - Decreased ovarian weight, ovarian follicular cysts and follicular atresia in rats - Mammary gland galactoceles in rats - Uterine cystic endometrial dilatation in rats and monkeys - Increased weight and hypertrophy of zona fasciculata of adrenals in rats and monkeys	These observations are of no relevance to humans: - Effects observed after repeated daily dosing at doses providing exposure to ulipristal acetate considerably higher than that reached clinically after a single 30mg dose. - Careful monitoring in clinical studies has revealed no relevant increase in adrenocorticotropic hormone (ACTH) or prolactin in patients taking ulipristal acetate 30 mg for emergency contraception and no symptoms of adrenal insufficiency. Similarly serum cortisol and prolactin were not modified after continuous intake of ulipristal acetate for 3 months at doses up to 10 mg (HRA2914-510).
• **Reproductive toxicity** **Prevention of pregnancy maintenance:** Repeated administration of ulipristal acetate prevented pregnancy maintenance in rats, rabbits, guinea pigs and monkeys as a consequence of its anti-progesterone activity.	Based on the doses which have been shown in animals to impair the maintenance of pregnancy, it is very unlikely to be of consequence in women after a single 30 mg dose of ulipristal acetate. This is reinforced by the available clinical and post-marketing evidence.
• **Developmental toxicity** **Embryofoetal development:** In rats and rabbits, the NOEL for maternal toxicity was 1 mg/kg/ day and that for developmental toxicology was 0.3 mg/kg/day;	These findings suggest that in case a woman is exposed to a 30 mgdose of ulipristal acetate early during her pregnancy, no deleterious effects on the fetal development is expected.

the 1 mg/kg/day dose caused some embryofoetal deaths but foetuses which survived developed normally. There was no indication of teratogenicity of ulipristal acetate in any of these studies. In the pharmacological study conducted in monkeys, administration of ulipristal acetate prevented pregnancy maintenance in some but not all animals. In the animals in which pregnancy continued, there were no structural or physiological anomalies in foetuses or infants.	
Pre-post natal development: The F1 generation of pups from rats which had been treated in the early days after mating was followed including their reproductive capacity and no adverse effects were observed. Similarly the physical development, learning capacities, performance in behavioural tests, as well as the sexual maturation, mating performance and fertility of the F1 generation of pups from rats which had been treated from the day 6 of gestation through to weaning, were followed up.	These results are in agreement with those from the embryofoetal development studies in rats and rabbits and the pharmacology study in monkeys which showed that no adverse effects are expected on foetuses or offspring of women in whom the 30mg dose did not have the intended contraceptive effect and who continued with their pregnancies.
• **Nephrotoxicity** Increased kidney weight in the monkey toxicity study that was not associated with any clinical pathology or histopathological correlate.	Haematological or blood protein parameters as well as parameters of renal function have been investigated in all pharmacodynamics studies and in a subset of subjects (approximately 170 at baseline and 150 at the end of study) in the Phase III study (HRA2914-509). No clinically relevant findings were reported.
• **Hepatotoxicity** Increase weight associated with hepatocyte hypertrophy was only observed in rat studies (14-day and 6 months) at doses of 100 and 25 mg/kg respectively. No liver changes were observed in other toxicity studies including the 6-month study conducted in monkeys. In addition liver enzymes in this species were either decreased (ALT) or not modified (GGT, AST).	This effect was interpreted as an adaptative response to the increased metabolic load imposed by daily administration of ulipristal acetate. This is a very common finding in toxicology studies for compounds that are metabolized by the liver, and thus, this finding is unlikely to be of relevance in humans. During clinical studies, there was no signal of liver toxicity in relation to ulipristal acetate exposure.
• **Genotoxicity**	

There was no indication of any genotoxic potential in any of the battery of tests performed *in vitro* and *in vivo*	
• **Carcinogenicity**	
Two carcinogenicity studies were conducted in rat (PGL09-005) and mice (PGL10-005) in the frame of development of Ulipristal acetate 5 mg tablets in uterin fibroids indication.	The carcinogenicity studies were assessed in Esmya procedure EMEA/H/C/2041/II/0014. It was concluded that ulipristal is not carcinogenic in experimental animals at sufficiently large exposure margins compared to human exposure.
• **General safety pharmacology:**	
Cardiovascular (including potential for QT interval prolongation)	
After oral administration to conscious dogs, isolated increase in blood pressure was observed at 25 and 125mg/kg doses, but there were no effects on ECG (RR, PR, QT, QTcF, QTcQ intervals or QRS duration). This is consistent with ulipristal acetate lack of effect on action potentials in isolated Purkinje fibres or HERG tails current.	The exposures achieved in these studies are far in excess (more than 130-fold higher) of those reached in women after a single 30mg dose of ulipristal acetate; the increase in blood pressure observed in dogs was isolated without any other cardiovascular effect and is unlikely to be of relevance in humans.
Nervous system	
Effects of ulipristal acetate on behavior were investigated in rats (Irwin tests)	No significant gross behavioural of physiological changes were observed at doses up to 125 mg/kg.
• **Mechanism for drug interactions**	
Ulipristal acetate is predominantly metabolized by CYP3A. Co-administration with CYP3A4 inhibitors may therefore increase exposure to ulipristal acetate.	Two DDI *in vivo* studies were performed to describe this interaction with a potent CYP3A4 inhibitor ketoconazole and a moderate CYP3A4 inhibitor erythromycin (Study HRA2914-547 and HRA2914-549). The *in vivo* concomitant use of the CYP3A4 inhibitors ketoconazole and erythromycin at therapeutic doses and ulipristal acetate led to increased exposure of ulipristal acetate and its main active metabolite which are unlikely to have any clinical consequences for a single dose administration.
Similarly co-administration with CYP3A4 inducers may decrease exposure to ulipristal acetate.	Concomitant use of ulipristal acetate with CYP3A4 inducers is a potential important risk for lack of efficacy
Ulipristal acetate and CDB-3877 did not demonstrate ability to induce CYP1A2 and CYP3A4 using fresh hepatocytes. Ulipristal acetate was not found to inhibit the activity of CYP1A2, CYP2C19 or CYP2E1 at the	These effects were observed at doses that are not clinically relevant. It is therefore concluded that ulipristal acetate is unlikely to participate in drug drug interaction with products that are metabolized by the CYP enzymes listed.

concentrations of (~5-50 µg/ml). Weak inhibition of CYP2B6 and CYP2C8 was observed for ulipristal acetate with IC50 walues >30µM and 22µM respectively. Weak inhibition on these CYP enzymes was also demonstrated for CDB3877 (ulipristal acetate main active metabolite) at concentration >20µM and 4µM respectively. Ulipristal acetate, but not CDB-3877, inhibits (>50%) CYP2C9, CYP2D6 and CYP3A4 activity, but only at the highest concentration tested (~50 µg/ml).	
Interaction effects of ulipristal acetate and its main metabolite CDB-3877 on P-gP transporters were investigated in Caco-2 cells. *In vitro* study showed that ulipristal acetate has an inhibitory activity on P-gP transporters, with an IC50 of 0.73 µM.	A clinical DDI study (HRA2914-548) was performed to investigate interaction of ulipristal acetate with fexofenadine, a P-gp substrate. No changes in the PK parameters of fexofenadine were observed. It was therefore concluded co-administration of ulipristal acetate is not expected to affect the pharmacokinetics of P-gp substrates and should not be expected to result in a clinically relevant effect.
Other toxicity-related information or data	NA

SII.1. Conclusions on non-clinical data

Safety concerns
Important identified risks (confirmed by clinical data) - none
Important potential risks (not refuted by clinical data or which are of unknown significance) • Interaction with CYP3A4 inducers
Missing information - none

PART II MODULE SIII: CLINICAL TRIAL EXPOSURE

SIII.1 Brief overview of development

The Phase I clinical program was initiated by NICHD (*United States National Institute of Child Health and Human Development*) and confirmed in humans the pharmacological characteristics of ulipristal acetate, specifically dose-dependent inhibition of ovulation.

The Phase I program was taken further by HRA Pharma, specifically to investigate the pharmacokinetic and pharmacodynamic profile of ulipristal acetate in clinical circumstances essential for EC use. Specifically, an additional pharmacodynamic study describing late follicular phase intake, a food effect, a lactation and four drug-drug interaction studies were conducted.

Two clinical Phase II and two clinical Phase III studies are available to document efficacy, safety and tolerability of ulipristal acetate in the indication emergency contraception.

The main Phase II trial (conducted by NICHD) was a double-blind comparative trial of ulipristal acetate (50 mg unmicronized capsule) versus levonorgestrel (0.75 mg twice) when used within 72 hours of intercourse. This trial showed that the efficacy of ulipristal acetate dose was statistically non-inferior to the reference product based on a non-inferiority margin of 2%, and the results showed a trend towards greater effectiveness of ulipristal acetate in comparison to levonorgestrel.

The Phase III clinical program comprised two studies designed to confirm the efficacy, safety and tolerability of the final, 30 mg micronized tablet dosage form in women who requested EC up to 120 hours after unprotected intercourse: one multicenter open-label study, and one multicenter randomized controlled trial with levonorgestrel 1.5 mg as the comparator.

The results of the two trials were consistent and statistically conclusive: ulipristal acetate significantly decreased the risk of pregancy after unprotected intercourse, from an estimated expected pregnancy rate of 5.5% to observed pregnancy rates of 2.1% (95%CI [1.41-3.10]) in the open-label study and 1.5% (95%CI [0.62-3.32%]) in the comparative study. The observed pregnancy rate in the levonorgestrel comparator group was 2.8% (95%CI [1.54-4.97]).

When the data from the two randomized trials that included a levonorgestrel comparator were combined into a pooled analysis, the results showed that ulipristal acetate prevented significantly more pregnancies than levonorgestrel.

There were no significant safety issues reported in Phase II or Phase III trials. Ulipristal acetate was well tolerated by the majority of subjects with adverse events associated with the treatment similar in type, severity and frequency to the comparator levonorgestrel.

SIII.2 Clinical Trial exposure

All of the subjects exposed to ulipristal acetate during clinical development prior to the Marketing Authorization were evaluated for safety.

Table 1 **Duration of exposure** (by indication and totals)		
Indication: Emergency contraception		
Duration of exposure (at least)	Persons	Person time
Single dose phase I (1 to 200 mg)	327	N/A
Daily dose phase I 84 days	35	N/A
Single dose phase II 10 or 50 mg	1858	N/A
Single dose phase III 30 mg	2637	N/A
Total exposure	4857	N/A

Table 2 **By dose** (by indication and totals)		
Indication: Emergency contraception		
Dose	Persons	Person time
1 to 200 mg phase I	327	N/A
2.5, 5 and 10 mg/d phase I	35	N/A
10 or 50 mg phase II	1858	N/A
30 mg phase III	2637	N/A
Total	4857	N/A

Table 3 **By age group and gender** (by indication and totals)				
Indication: Emergency contraception				
Age group	Persons		Person time	
	M	F	M	F
< 18	N/A	41	N/A	N/A
18-35	N/A	4529	N/A	N/A
>35	N/A	252	N/A	N/A
Total	N/A	4822	N/A	N/A

Table 4 **By ethnic or racial origin** (by indication and totals) in phase II and III studies		
Indication: Emergency contraception		
Ethnic/racial origin	Persons	Person time
Caucasian	3020	N/A
Black	813	N/A
Asian	144	N/A
Other	411	N/A
Total	4388	N/A

PART II MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Subjects included in the Phase II and III studies were women requesting emergency contraception. Main exclusion criteria for the studies are provided below.

Phase II studies (HRA 2914-507, HRA 2914-508)
Main exclusion criteria:

- < 18 years
- Pregnant at screening or enrolment (positive high-sensitivity urine pregnancy test)
- Had been pregnant or breast-feeding within the 2 months prior to screening and enrolment
- Had used hormonal methods of contraception during the enrolment cycle or previous two cycles
- For women with recent history of Depo Provera use, most recent injection less than 9 months before study entry and not followed by at least one complete menstrual cycle (2 menses)
- Less than one complete menstrual cycle (2 menses) post miscarriage, delivery or abortion
- Had irregular menstrual cycles, as defined in the inclusion criteria
- Had experience nausea and vomiting within the 2 weeks prior to screening and enrolment
- Had impaired hypothalamic-pituitary-adrenal reserve or had received oral glucocorticoid replacement therapy in the year prior to screening and enrolment
- Not willing to abstain from further acts of unprotected intercourse during the study and until pregnancy status has been ascertained

Phase III studies (HRA 2914-509, HRA 2914-513)
Main exclusion criteria:

- < 16 years
- One or more acts of one unprotected intercourse more than 120 hours before requesting emergency contraception in the current cycle
- Currently pregnant as confirmed by positive HSUP test performed at screening (treatment visit)
- Currently breast-feeding
- Current use of hormonal contraception
- Use of hormonal emergency contraception since last menstrual period
- Severe asthma insufficiently controlled by oral glucocorticoid

SIV.1. Limitations of ADR detection common to clinical trial development programmes

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare (it may be appropriate to choose other ADR frequencies)	More than 4,000 subjects were exposed in clinical trials.	ADRS with a frequency greater than 1 in 1,000 could be detected if there were no background incidence
Due to prolonged exposure	No prolonged exposure has been studied.	The single dose posology should not lead to prolonged exposure under usual circumstances.
Due to cumulative effects	No cumulative effect was studied.	The single dose posology should not lead to cumulative effects under usual

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
		circumstances. Data were made available on repeated use and this safety concern is discussed in section SIV4 and considered for removal from missing information
Which have a long latency	No long term effects were studied.	No long term effects are expected.

SIV.2. Effect of exclusion criteria in the clinical trial development plan

Exclusion criteria which will remain as contraindications	
Criteria	**Implications for target population**
None	Not applicable

Exclusion criteria which are NOT proposed to remain as contraindications		
Criteria	**Reason for being an exclusion criterion**	**Justification for not being a contraindication**
Age < 18 years	Parents informed consent needed in most countries	EC should not be a contraindication in the target population that include young women
Had been pregnant or breast-feeding within the 2 months prior to screening and enrolment	Bias to assess efficacy due to decreased fertility and safety (no data were available on the excretion of UPA in milk at the time of the studies. UPA, as a lipophilic compound, was thought to be theoretically excreted in breast milk)	No need to contraindicate. Breast-feeding recommendations are included in the SPC section 4.6.
Less than one complete menstrual cycle (2 menses) post miscarriage, delivery or abortion	No valid baseline information on bleeding available, bias in the evaluation of bleeding and safety after treatment intake	No need to contraindicate in the target population
Had used hormonal methods of contraception during the enrolment cycle or previous two cycles or Depot Provera less than 9 months prior to enrolment	Bias to assess efficacy and safety	No need to contraindicate
Not willing to abstain from further acts of unprotected intercourse during the study and until pregnancy status has been ascertained	Bias in efficacy assessment	No need to contraindicate
Had irregular menstrual cycles, as defined in the inclusion criteria	Bias to assess efficacy and safety	No need to contraindicate

Exclusion criteria which are NOT proposed to remain as contraindications		
Criteria	**Reason for being an exclusion criterion**	**Justification for not being a contraindication**
Had experienced nausea and vomiting within the 2 weeks prior to screening and enrolment	Bias to assess efficacy and safety	No need to contraindicate
Had impaired hypothalamic-pituitary-adrenal reserve or had received oral glucocorticoid replacement therapy in the year prior to screening and enrolment	Bias to assess efficacy and safety since ulipristal acetate has high affinity for the glucocorticoids receptors.	No need to contraindicate
One or more acts of one unprotected intercourse more than 120 hours before requesting emergency contraception in the current cycle	Bias to assess efficacy and safety	Out of the indication

SIV.3. Limitations in respect to populations typically under-represented in clinical trial development programmes

Children

Forty-one women aged less than 18 were enrolled in the Phase III studies.

Safety in post pubertal children is being addressed within the Paediatric Investigation Plan which was approved in March 2009 by the PDCO. Two hundred and seventy nine (279) women under 18 and 76 under 16 (on a total of 579) were included in the study (HRA2914-515) presented in section SIV.4.

Men or elderly

Due to the indication, ulipristal acetate has not been studied in men or elderly.

Women of childbearing potential

Due to the claimed indication, all the subjects enrolled in all the clinical trials were women of childbearing age.

Pregnancy

In the population treated with ulipristal acetate during the overall clinical development of ulipristal acetate in emergency contraception performed by HRA Pharma, a total of 92 women became pregnant.

The pregnancy outcome is indicated below:

- Induced abortion: 60
- Spontaneous abortion: 15
- Live birth: 7
- Lost to follow-up: 10 (including 5 who declared prior to being lost to follow-up that they intended to carry their pregnancy to term)

In addition, information is available from HRA Pharma's partner Preglem which developed and now markets ulipristal acetate 5 mg tablet (Esmya) for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age (cf. PSUR 3 Ulipristal

acetate 30 mg tablet). A patient received 20 mg daily of ulipristal acetate for 10 days (corresponding to a total exposure of 180 mg) between the fourth and fifth week of amenorrhea of a gemellar pregnancy. Delivery took place on [redacted] 2010 and led to two normal babies.

Another pregnancy was also reported during a trial during the development of ulipristal acetate for the treatment of uterine fibroids. A 27 year old woman took ulipristal acetate 10 mg daily for 8 days (18-25 May 2012) before a pregnancy was diagnosed at 6 weeks gestation. The treatment was then stopped and the subject was lost to follow-up. This pregnancy is described in the PSUR N°1 received from Gedeon Richter submitted to EMA on October 26th, 2012.

Repeated use

In the phase II trials, four multiple enrolments were reported; no specific analysis has been performed. In the phase III studies, 84 women took ulipristal acetate on multiple occasions. Multiple enrolments occurred in the same menstrual cycle only in 5 women. There were no differences in the repeat enrollers in terms of incidence or severity of adverse events. A specific study examined the effect of repeated doses of 30 mg UPA (weekly or every 5 days for 8 consecutive weeks) on ovulation, the menstrual cycle parameters, and safety parameters (HRA2914-554). No safety issues arose in this study in which subjects received eight to ten 30 mg doses.

Lactating women

No data were available on ulipristal acetate excretion in milk from the pre authorization phase. Since the presence of ulipristal acetate in milk has been detected in lactating female rats, HRA Pharma has performed a pharmacokinetic study in 12 lactating women in [redacted] The results of study HRA2914-514 (lactation study) showed that ulipristal acetate and monodemethylated-ulipristal acetate passed rapidly into breast milk after ulipristal acetate intake and are excreted with approximately 77% of excretion in the milk occurring within the first 24 hours, 90% within 48 hours, 95% within 72 hours and 98% within 96 hours after dosing. Ulipristal acetate was safe and well tolerated in lactating women. The effect of ulipristal acetate on newborns/infants has not been studied. However, given the mechanism of action of UPA and as there is no role for progesterone in the newborn infant, it is unlikely to have any detrimental effects on the new born infant if ingested in breast milk but because of lack of evidence, a risk to the breastfed child cannot be excluded.

A variation was submitted in July 2012 to propose an update of the product information to reflect the results of this study. The section 4.6 of the SPC was updated accordingly and specifies that "*After intake of ellaOne breastfeeding is not recommended for one week. During this time it is recommended to express and discard the breast milk in order to stimulate lactation.*"

Overweight and obese women

There was no limitation in the phase III clinical trials in the development program.

Patients with hepatic impairment

The safety of ulipristal acetate has not been evaluated in patients with hepatic impairment.

Patients with renal impairment

The safety of ulipristal acetate has not been evaluated in patients with renal impairment.

The renal excretion of ulipristal acetate after a single dose administration is very limited (6%). No increase of exposure would be expected in case of renal impairment. As there is no

possibility of accumulation and increased plasma concentration, the MAH considers there is no need to evaluate the safety of ulipristal acetate in patients with renal impairment.

Patients with other relevant co-morbidity

Not applicable.

Patients with a disease severity different from the inclusion criteria in the clinical trial population

Not applicable.

Sub-populations carrying known and relevant polymorphisms

Not applicable.

Patients of different racial and/or ethnic origin

As indicated in Table 4, 813 Black/African Americans and Asians have been exposed to ulipristal acetate during the Phase II/ III trials.

It is considered that the safety in this subgroup of population has been adequately assessed.

SIV.4. Conclusions on the populations not-studied and other limitations of the clinical trial development programme

Missing information

Safety concerns due to limitations of the clinical trial programme		**Outstanding concern?**
Safety concern	**Comment**	**Yes/No**
Effects in post pubertal children	Under routine monitoring Data were obtained from the PIP study and this safety concern is discussed below and considered for removal from missing information	No
Effects on foetus and newborn	Under routine monitoring This safety concern is an important potential risk and is discussed in section S.VII.3	Yes
Effect of concomitant use of progestin-only contraception	Under routine monitoring	Yes
Effect in patients with severe asthma treated by oral glucocorticoid	Under routine monitoring	Yes
Effects in women with impaired liver function	Under routine monitoring	Yes
Efficacy and safety in repeated use in the same cycle	Under routine monitoring Data were made available on repeated use and this safety concern is discussed below and	No

	considered for removal from missing information	

Considering the exclusion data for clinical trials, the population not studied and limitations of the clinical trials, the following topics had been considered as missing information in the RMP. Each one is discussed in light of the most current information available:

1. Effects in post pubertal children

Observational study HRA2914-515 ('Steella') with completed active treatment part and ongoing preparation of CSR was a part of the PIP (see Appendix A9). Between 15 December 2010 and 18 January 2013, 579 subjects were enrolled, of whose 279 being under 18 years and 76 under 16 years of age. There was no statistically significant difference between subjects under 18 years of age and subjects aged 18 years and older regarding the intensity (p=0.302) and time of occurrence of AEs (p=0.106). AEs 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.

The most frequently reported TEAEs were headache, nausea abdominal pain, with similar incidence in the different age classes. Upper abdominal pain was reported 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].

Dysmenorrhea 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. Menorrhagia 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.

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.

Eight serious events of unintended pregnancy in adolescents were received during the interval reporting period, of which five ended in elective abortion. Five serious events of ulipristal acetate 30 mg tablet lack of efficacy (PT 'Drug ineffective') were reported and one serious event of off-label use (prescription of ulipristal acetate 30 mg tablet seven days after UPI). Four additional serious events were reported – vaginal haemorrhage, viral infection, uterine dilatation and curettage, and drug exposure during pregnancy.

Non-serious AEs included labelled headache (7 cases), abdominal pain (4), migraine (1), nausea (3), dizziness (2), vaginal discharge (1), and dysmenorrhea (2). Only one unlisted non-serious AE, breast pain, was reported in two cases.

Received reports are not suggestive of new safety-related patterns or trends.

Based on these results (safety analysis performed on 579 women, of whose 279 being under 18 years, the MAH considers that "effect in post pubertal children" is no longer missing information.

2. Effect of concomitant use of progestin only contraception

Ulipristal acetate is a progesterone receptor modulator with antagonistic activities. Because ulipristal acetate binds the progesterone receptor with high affinity, it may in theory interfere with the action of progestin-only contraceptives (including levonorgestrel emergency contraception) and therefore contraceptive action could in theory be altered.

Women may need to use EC if they have missed a contraceptive pill. As stated in the SPC, the use of ellaOne does not contraindicate the continued use of regular hormonal contraception but after using ellaOne, it is recommended that subsequent acts of intercourse be protected by a reliable barrier method until the next period starts.

The likelihood that both EC methods would be used concurrently is theoretical since such use has never been recommended. Nevertheless such concomitant use is clearly stated as not recommended.

These interactions are mentioned and appropriate recommendations are given in sections 4.4 and 4.5 of the SPC and in the package leaflet (see Appendix A2).

3. Effect in patients with severe asthma treated by oral glucocorticoid

Ulipristal acetate binds with moderate affinity to the glucocorticoid receptor and may therefore interfere with the action of glucocorticoid treatments. This might be relevant in case of severe asthma treated by oral glucocorticoid. The potential impact on individual patient or on public health is considered as low for this risk considering the single administration of ulipristal acetate and since this association is mentioned as not recommended in the SPC (section 4.4) and the package leaflet.

No interaction with products interacting with the glucocorticoid receptor has been reported as adverse reaction since the launch of ellaOne.

4. Effects in women with impaired liver function

Regarding the effects in women with impaired liver function, the SPC and package leaflet mention the absence of specific studies in these specific populations and the use in patients with severe hepatic impairment is not recommended.

5. Efficacy and safety in repeated use in the same cycle

In the previous RMP (version 12), "efficacy and safety in repeated use in the same cycle" was mentioned as missing information. Because new data are made available on repeated use, the MAH is of the opinion that this risk is no more to be controlled through the risk management system as missing information and propose to remove this safety concern from the missing information.

Study HRA2914-554 investigated the effect on safety parameters of ulipristal acetate 30 mg administered once weekly (Q7D) or once every 5 days (Q5D) for 8 weeks in 23 healthy subjects whose mean age was 30.3 years. A total of 68 treatment-emergent AE were reported by 22 subjects (95.7%). The most frequently reported TEAE was headache in 10 subjects (43.5%). TEAEs were reported with similar incidence in the 2 treatment arms (91.7% and 100% for Q7D and Q5D arms, respectively). No SAE was reported. All TEAEs were of mild or moderate intensity. The most frequent suspected treatment-related AE was headache (13%). In general,

subjects did not have clinically relevant shifts in biochemical parameters including clinical chemistry, hematology or VTE markers during the study, nor were there any notable differences between treatment arms. UPA was well tolerated in both treatment arms and, no safety issue arose in this study in which subjects received eight to ten 30-mg doses, in comparison to the profile established for a single 30 mg dose.

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. Following an initial period during which follicular activity was delayed, after 3 to 6 doses, ovulation occurred in a majority of subjects. When ovulation occurred, physiological and hormonal characteristics indicated that it was physiological. The PD effects seen in this study mirrored those observed with single doses of ulipristal acetate administered at different times in the cycle (studies HRA2914-509 and HRA2914-513).

Altogether ulipristal acetate was well tolerated in both treatment arms and, importantly, no new safety issues arose in this study in which subjects received eight to ten 30 mg doses, in comparison to the profile established for a single 30 mg dose. Although emergency contraception is not intended to be used repeatedly, situations may arise in which women find themselves in need, more than once in a given cycle. The results of this study suggested that ulipristal acetate 30 mg could be safely administered if needed more than once in a given menstrual cycle for emergency contraception.

PART II MODULE SV: POST-AUTHORISATION EXPERIENCE

As of 14 May 2014, it is estimated than more than 2.3 million women have taken ellaOne. In post-marketing setting, 851 Individual Case Safety Reports (ICSRS) have been collected. Among these spontaneous and solicited reports received, four hundred and fourty one (441) were pregnancy reports (corresponding to 442 outcomes since there was a birth of healthy twins). These 441 reports included fourty (40) reports of inadvertent exposure during pregnancy, 172 reports of lack of efficacy and 229 reports of unintended pregnancies when pregnancy status was unknown at ellaOne intake.

The majority of the pregnancy reports (88.2%) were medically confirmed.

As mentioned in the following table, 35 pregnancies had an outcome of 36 live births since there was a birth of twins. Among these 36 live births, two occurred further to inadvertent exposure to ulipristal acetate.

Pregnancy outcome	**Number of post-marketing pregnancy cases****					
	Total	**Timing of exposure**				
		Before conception	**1st trimester**	**Potential failure with lack of information excluding an ongoing pregnancy started prior to UPA intake**	**Potential failure with available information about pregnancy age estimation**	**Unclassified**
Unknown outcome*	184	47	14	41	3	79
Ongoing	22	10	2	8	1	1
Ectopic pregnancy	10	5	0	4	0	1
Spontaneous miscarriage	30	17	2	4	0	7
Elective termination	160	73	20	19	22	26
Live birth	35	20	2	6	2	5
Total	**441**	**172**	**40**	**82**	**28**	**119**

** Lost to follow-up.*
***Includes cases of inadvertent exposure during pregnancy, pregnancies resulting from a Lack of Efficacy or potential lack of efficacy*

One case of trisomy 21 was reported during the period of PSUR 6. It was a case of drug exposure in a 42-year old woman during pregnancy considered as unlikely related to ellaOne since the patient was at 6 weeks and 2 days of amenorrhea when she took the drug.

One case of foetal cardiac defect discovered at 12 weeks of pregnancy was received from health authorities; it concerned a 18-year old woman who experienced vaginal spotting fourteen days after ellaOne intake and starting of desogestrel/ethinylestradiol. A pregnancy termination was performed at 13 weeks. The relationship to ellaOne was assessed as uncertain by the reporter. Further information has been requested for this case and is still pending.

One case of live birth of a boy with neonatal complications: hypoxic ischaemic encephalopathy: this case of foetal neonatal distress occurred at 40 weeks and 3 days of gestation in an otherwise uneventful pregnancy. The mother was 34-year old and had used ellaOne in the conception cycle (she was not pregnant at the time of intake) during an observational study performed in [redacted] The baby was in persistent occiput posterior position at the time of delivery and a C-

section was performed due to foetal distress. The infant suffered from hypoxic ischemic encephalopathy, left epidural haematoma and multiple parenchymal haematomas. A causal relationship between this complication of delivery and ellaOne intake more than 8 months prior is unlikely as this adverse foetal outcome is the consequence of a delivery complication and associated neonatal distress.

One case of Beckwith-Wiedemann syndrome was reported during the period of PSUR 8. It concerned a 30-year old mother with a history of one previous [redacted] with no alcohol, cigarettes or illicit drugs addiction, who was pregnant after ellaOne intake 17 days after LMP for post-coital contraception. The mother experienced pre-term premature rupture of membranes in week 31+2 days and gave birth to a male neonate diagnosed with Beckwith-Wiedemann syndrome. The infant at birth weighed 2320 g, length 49 cm. Hypoglycemia after birth, macroglossia, small umbilical hernia, diastases recti, large-for-age, nephromegaly and muscular hypotonia led to the diagnosis of a Beckwith-Wiedemann syndrome, later confirmed by molecular genetic analysis. The development of the child was delayed. The patient was also exposed in utero to Clexane 80 mg (enoxaparin) for mother's pelvic venous thrombosis from gestational week 24 to birth, and folic acid for prophylaxis of neural tube defect, from gestational week 6 to birth. A causal relationship between the reaction and ellaOne cannot be formally excluded; however, no similar reports were received and considering the available data, no medical conclusion can be drawn.

One case of diaphragmatic aplasia and cardiopathy of the foetus was reported during the period of PSUR 8. It concerned a 39-year old woman, with two normal previous pregnancies. On pregnancy week 22, a level two ultrasound revealed diaphragmatic aplasia and cardiopathy of the foetus, leading to an [redacted] The woman was concomitantly treated with diclofenac, taken occasionally during pregnancy as anti-inflammatory, ferrous and folic acid (dose, indication and time of exposure not specified). No medical conclusion could be drawn on ellaOne causal role, based on the provided data.

Ten cases of ectopic pregnancy were reported, that are detailed in section SVII.3.

The reported frequency of spontaneous abortions (11.7%) in post-marketing setting (i.e. thirty spontaneous abortions out of 257 reports with known outcome on 441), including two in women inadvertently exposed to ellaOne during pregnancy, is below what occurs in the general population since the incidence among clinical pregnancies is about 12-15% but including early pregnancy losses it is 17-22% (Garcia, 2002). In post-marketing surveillance, no haemorrhagic event or other relevant signal has been reported which could have suggested an increase in incomplete miscarriage.

Sixteen case reports of use during breastfeeding were collected, but no adverse reaction has been reported in the breastfed babies.

No signal has been detected from pre-existing pregnancies exposed to treatment or live births reported from clinical trials and post-marketing surveillance.

SV.1 Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons

There were no actions taken for safety reasons since the authorisation of ellaOne.

SV.2 Non-study post-authorisation exposure

SV.2.1 Method used to calculate exposure

According to the marketed product presentation, indication and the recommended dosage (one administration per cycle of one single tablet), it is reasonable to assume that each patient has received only one treatment within the period allowing to consider that patient exposure equals the number of packs sold.

SV.2.2 Exposure

ellaOne was first launched in Europe on 1 October 2009; the total number of women exposed worldwide as of 30 April 2014 is estimated at 2,343,765 (Source: sales data from company and its partners).

SV.3 Post-authorisation use in special populations

Not applicable.

SV.4 Post authorisation off-label use

An off-label use survey (FUM008 – HRA2914-544, 544a and HRA2914-552), agreed upon with EMA as a post-marketing requirement was performed in 2012 and 2013. This survey was aimed at characterizing and quantifying off-label prescriptions of ellaOne in European countries.

It was carried out using a two-step approach (MEA 008) with a qualitative and quantitative phase in selected European countries representative of the various context of EC level of use and abortion access: France, Germany, Poland, Portugal, Sweden and UK.

The results of this survey (qualitative and quantitative phases) did not identify any signal of attempted use of ellaOne to terminate an ongoing pregnancy. In comparison to results obtained for levonorgestrel, there is no indication of higher rate of any off-label use associated with ellaOne.

Nevertheless, the relatively high percentages of prescription beyond 5 days in Poland and Sweden (Poland 31% (n=13) and in Sweden 34.5% (n=10)) resulted from the quantitative questionnaire was not explained. As the percentages were not in line with those reported for some other countries, it was suggested by the CHMP that sampling error might be the reason for such differences. The MAH was requested to repeat the study in the two countries Poland and Sweden, with a new set of participating prescribers and to investigate the reasons for prescribing ulipristal acetate 30 mg off label.

HRA Pharma repeated the questionnaire in Poland and Sweden utilizing a new sample of HCPs. The questionnaire was updated with questions that verify the reason for prescribing ulipristal acetate 30 mg off label.

The repeat study (HRA2914-544a) did not show an increased rate of off label in Poland or Sweden. In both countries, 20% of prescribers recalled to have prescribed at least once ulipristal acetate 30 mg more than 5 days after the unprotected intercourse. This finding is in line with the percentages found in the other countries. These percentages are also in line with the percentages of physicians who reported at least once the prescription of levonorgestrel more than 3 days after the unprotected intercourse.

The frequency of and reasons for these off label prescriptions have been assessed. When a prescriber indicated to have prescribed more than 5 days after UPI, this happened between 1 to 3 times. The main reason for prescription more than 5 days after UPI was the uncertainty about the date of the unprotected intercourse.

Additional reasons that were clearly expressed are the fear of the women to become pregnant in combination with the idea that the product might still prevent a pregnancy even if taken more than 5 days after UPI.

No off label prescriptions were reported to have any relationship with intent to terminate an existing pregnancy.

In conclusion, the results of the survey (qualitative and quantitative phases) did not identify any signal of attempted use of ulipristal acetate 30 mg to terminate an ongoing pregnancy. Results of these studies were assessed by the PRAC who agreed that the data were satisfactory to fulfill this Post-Authorisation Commitment (PAC No. MEA/008.8 fulfilled by CHMP opinion dated 20/09/2013).

In post-marketing setting, 35 spontaneous reports of off label use were retrieved from the database until 14 May 2014. They are summarised as follows:

- In 32 cases ellaOne was used beyond 120 hours after the unprotected intercourse.

  - In three cases, a pregnancy was reported: in one case, ellaOne was prescribed 7 days after an unprotected intercourse, in another case, ellaOne was prescribed 8 days after unprotected intercourse; in the third case, ellaOne was prescribed 9 days after unprotected intercourse. No other information was provided for these cases despite several attempts to gather further information.
  - In 27 cases (collected from physicians in market survey), ellaOne was prescribed between 120 hours and seven days after an unprotected intercourse No other information was provided and the physicians mentioned that the subjects were lost to follow up.
  - Two cases were received from spontaneous pharmacovigilance reporting. For one case (received from a consumer) ellaOne was prescribed 140 hours after UPI and the woman experienced breast pain, vaginal haemorrhage, and breast tenderness. For the other report (received via a pharmacist), the woman forgot one pill of her regular contraception and took ellaOne more than five days after UPI.

- In one case, a woman took one tablet of ellaOne the day of her pregnancy diagnosis, 30 days after unprotected intercourse, as she was 3-week pregnant. The case from [redacted] was received via the pregnancy registry. No other information was provided.

- In one case, ellaOne was taken by a man. Headache, vomiting and hyperhidrosis were reported. The man and his 16-year old girlfriend went to a pharmacy with a prescription for ellaOne and were informed about the product.

- In one case, ellaOne was taken by a 8-year old girl. She was prescribed ellaOne by a gynecologist, for assumed [redacted] No other information was provided.

SV.5 Epidemiological study exposure

Study title and study type	Objectives	Population studied	Duration	Number of persons	Comment
Prescription survey to evaluate the perception, the use and the potential off-label use of ellaOne (face-to-face or telephone in-depth interviews)	Evaluate condition of prescription of ellaOne and potential off-label use Assess safety of ellaOne Evaluate the general perception of ellaOne among ellaOne's prescribers	Primarily gynecologists but also general practioners, clinicians, nurses. All involved in the prescribtion or delivery of EC In 6 European countries	Participants were recruited in March and April 2011	90 health care providers	FUM008 HRA2914-544: Qualitative phase report Completed. PAC No. MEA/008.8 Fulfilled (CHMP opinion 20/09/2013)
Prescription survey to evaluate the perception, the use and the potential off-label use of ellaOne (data was collected anonysmously through a web based questionnaire)	Primary: Potential off-label use of ellaOne in Poland and Sweden. Secondary: assess the perception of ellaOne and the experience of its usage among EC prescribers /providers.	Gynecologists in Poland and Midwifes in Sweden. All involved in the prescription or delivery of EC.	Participants were recruited in May 2013	A total of 75 Healthcare providers (40 Gynecologists and 35 Midwifes)	FUM008 HRA2914-544a: Qualitative phase report Completed PAC No. MEA/008.8 Fulfilled (CHMP opinion 20/09/2013)
Prescription survey to evaluate the perception, the use and the potential off-label use of ellaOne (retrospective and cross-sectional survey of ellaOne prescribers/health care providers in Europe)	Primary: assess the potential off-label use of ellaOne Secondary: asses the perception of ellaOne and usage experience and compare ellaOne results with those of levonorgestrel	Primarily gynecologists but also general practioners, clinicians, nurses and midwifes All involved in the prescribtion or delivery of EC In 6 European countries	Participants were recruited between February 6 and March 30, 2012. The survey includes patients cases treated with ellaOne or levonorgestrel at any time between August 1, 2011 and March 30, 2012.	315 health care providers	FUM008 HRA2914-552: quantitative phase report Completed PAC No. MEA/008.8 Fulfilled (CHMP opinion 20/09/2013)

PART II MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1. Potential for harm from overdose

No case of overdose has been observed during the clinical development program.

In study HRA 2914-503, where single doses up to 200 mg have been administered, the 200 mg dose was well tolerated and no effect on cortisol or ACTH was observed.

The potential for overdose is limited because each box contains only one blister of one tablet.

SVI.2. Potential for transmission of infectious agents

Ulipristal acetate is a substance devoid of any risk of transmission of infectious agents since none of the components is of biological origin. The only excipient of the formulation of animal origin is lactose monohydrate, which is guaranteed to be free from bovine spongiform encephalopathy by the supplier.

SVI.3. Potential for misuse for illegal purposes

The profile of ulipristal acetate is not indicative of any potential for abuse.

SVI.4. Potential for medication errors

The name ellaOne has been approved by European Authority and is sufficiently different from other brand names to minimise the risk of confusion.

ellaOne is available in a single strength (30 mg) tablet, preventing any risk of confusion in terms of dose; the tablet is round, curved and engraved with "ella" on both sides, which minimises the risk of confusion with other products.

Each box contains only one blister of one tablet, which limits the risk of medication errors.

The package leaflet includes reminders on indication, contraindications, precautions and dosing recommendations.

SVI.4.1 Description of medication errors during the clinical trial programme

No medical errors were seen in clinical development programme.

SVI.4.2 Preventive measures for the final product(s) being marketed

Routine preventive measures were employed, including text and graphical design of packaging, drug naming, and instructions for use in PIL.

SVI.4.3 Effect of device failure

Not applicable.

SVI.4.4 Reports of medication errors with the marketed product(s)

In post-marketing setting, 30 cases of reported medication errors were retrieved from the database until 14 May 2014.

Ten reports were received further to administration of expired drug. In one case, abdominal pain was reported. No adverse drug reaction was reported in the nine other cases.

In one report, the tablet was chewed; no adverse drug reaction was reported.

Five cases of labelled drug-drug interaction medication error with levonorgestrel emergency contraception were reported. In three cases, pregnancy was reported. In one other case, menstrual disorder was reported. In the last case, delay of menstruation was reported.

Three cases of labelled drug-drug interaction medication error with regular hormonal contraception were reported. In one case, spontaneous abortion, heavy vaginal bleeding, nausea and stomachache were reported. In another case, vaginal haemorrhage was reported.

Four cases of exposure during breastfeeding were reported as medication error; no adverse drug reaction was reported.

Five cases of repeated use during same cycle were reported as medication error. In one case, nausea, chills, headache, back pain and delayed menstruation were reported. In another case where ellaOne was taken 3 times over 3 days, salpingo-oophoritis was reported. In one case where ellaOne was taken once a week during one month, no adverse drug reaction was reported. In one case, delayed menstruation was reported. In the last case where ellaOne was taken twice within 5 days, delayed menstruation was reported.

One report was a drug prescribing error associated with non serious menstrual disorder and hypomenorrhea and one report was an accidental intake by a 2.5 year old child for which no ADR was reported.

SVI.5. Potential for off-label use

In order to assess the nature and prevalence of any off-label practices with respect to emergency contraception prescription or use, HRA Pharma performed a survey among prescribers in six European countries (FUM 008, HRA2914-544) approximately two years after ellaOne launch. Over 1200 patient cases were reviewed, and situations of off-label use were detected in less than one percent of patients and were similar whether the emergency contraceptive was levonorgestrel or ellaOne. Off-label use of ellaOne was reported in eleven patients (0.9%) from six healthcare providers, and most frequently corresponded to use outside than the labelled time window (i.e., more than 120h after intercourse). Even though off-label use would appear rare in practice, three specific issues are reviewed here. An additional survey (FUM 008, HRA 2914-544a) was performed to further clarify potential off-label use in Sweden and Poland. Specific questions to understand reasons for potential off-label were asked. Together with the original study and in comparison to results obtained for levonorgestrel, there is no indication of higher rate of any evaluated off-label use associated with ellaOne. Results of these studies were assessed by the PRAC who agreed that the data were satisfactory to fulfill this Post-Authorisation Commitment (PAC No. MEA/008.8 fulfilled by CHMP opinion dated 20/09/2013).

Off-label use as regular contraception:

The extensive literature on pharmacy access to levonorgestrel has shown that women do not mistake emergency contraception for an ongoing method of contraception, nor do they use it intentionally and on a consistent basis instead of a regular method of contraception (Rowlands 2000, Raine 2005, Fairhurst 2004, Ziebland 2005). In HRA Pharma's decade-long post-marketing surveillance of its levonorgestrel product (which is available non-prescription in many countries of the European Union and elsewhere), no signal of use of emergency contraception as a regular method of contraception has been detected.

The potential for off-label use of ellaOne as regular contraception is also limited by the fact that ellaOne is only available in the form of single tablet packs. It is therefore highly unlikely that ellaOne would be used repeatedly as a method of regular contraception.

However, in order to minimize this risk, recommendations are made in the SPC (section 4.4) and in the PL.

Off-label use later than 5 days:

In the off-label use survey (FUM008 – HRA2914-544, 544a and HRA2914-552), the off-label use of ellaOne outside the approved 5-day time window was low across all countries. If prescription occurred outside of the 5 days time window, the reason was mainly the uncertainty over the date of the unprotected intercourse, and with the hope the product would still be able to postpone the ovulation. In no instance the prescription outside of the 5 day time-window happened with the intention to interrupt an existing pregnancy.

Another survey (BVA Healthcare 2012 – HRA2914-557) performed in five European countries showed that among 500 women who used emergency contraception in the past 12 months, the intake of EC more than five days after the unprotected intercourse was observed in about 1%. More than 80% of women take emergency contraception in the 24h following unprotected sex.

Deliberate intake during pregnancy:

ellaOne is a method of emergency contraception intended to prevent pregnancy; deliberate intake during pregnancy is clearly outside of the indication. A review of the literature shows that deliberate intake of emergency contraception during pregnancy is excessively rare. Indeed, no reports have been identified in the literature, and only three cases have been reported in post-marketing surveillance of over 70 million doses of levonorgestrel (HRA Pharma internal data). In post-marketing surveillance there has been one report of suspected deliberate intake of ellaOne during pregnancy, and in the off-label survey (FUM 008, HRA2914-544, 544a and HRA2914-552) no prescriptions were reported with the intend to terminate an existing pregnancy. Review of the patient cases did not reveil any concern that ellaOne would be used intentionally during pregnancy to attempt to interrupt pregnancy.

Because ellaOne is only available in the form of single tablet packs, the first scenario to consider is the intake of a single dose of ellaOne during pregnancy. Available data from both animals and clinical exposure indicate that pregnancy would not be affected. Indeed, the miscarriage rate in the ellaOne-exposed pregnancies database is inferior to that reported for the general population (11.7% vs 20%), demonstrating that a single dose of ellaOne will not interrupt pregnancy.

With respect to the deliberate intake of higher doses during pregnancy, only preclinical data is available. Data from experimental animal models have shown that a dose of 30 mg/animal/day for two consecutive days (corresponding to 70 mg/kg/day for two days) was required to interfere with gestation in pregnant guinea pigs, whilst a dose of 5 mg/kg/day for four days to pregnant monkeys, interrupted gestation in some but not all animals. Importantly, in animals in which pregnancy continued and which were allowed to deliver normally, there was no evidence of structural or physiological abnormalities in foetuses or infants.

Nevertheless, the following measures are applied to encourage correct use of ellaOne:

- Mention that pregnancy should be excluded before ellaOne is administered and that ellaOne does not interrupt a pregnancy (SPC section 4.2, 4.4 and 4.6)

- Avoid language in SmPC and PL that could be misunderstood that ellaOne could be used to interrupt a pregnancy.

Conclusion:

The potential for off-label use appears limited and does not appear to be a safety concern for ellaOne. Nevertheless in order to encourage correct use of ellaOne in a non-prescription setting, the Product Information cover key messages detailed above.

Off-label use reports are monitored through routine pharmacovigilance and are presented in the PSURs.

SVI.6. Specific Paediatric issues

SVI.6.1 Issues identified in paediatric investigation plans

PDCO decision EMEA-000305-PIP01-08 granted PIP deferral and waiver for ulipristal acetate.

Waiver applies to boys from birth to less than 18 years, and girls from birth to age at menarche.

Pre-clinical and clinical studies (in girls from menarche to less than 18 years) were agreed for PIP.

Modification of PIP has been accepted on 25 January 2010 (EMEA-000305-PIP01-08-M01) with postponment for completion to May 2012.

The second modification of PIP has been accepted in July 2011 (EMEA-000305-PIP01-08-M02), including postponment for completion of PIP till October 2013.

The PDCO adopted on 8 November 2013 an opinion confirming the compliance of all studies in the agreed paediatric investigation plan as set out in the latest Agency's Decision (P/198/2011).

ellaOne <EMEA-000305-PIP01-08-M02>		
Issue (safety or long term efficacy)	**Background**	**Relevance to indications covered in this RMP and how, if appropriate, it will be addressed.**
Concerns on potential safety issues in relations to paediatric use	Missing information on girls from age at menarche to less than 18 years	PIP non-clinical and clinical studies have been requested. The safety concern "Effects in postpubertal children" that was identified as missing information is proposed for removal (see section SIV.4).

SVI.6.2 Potential for paediatric off-label use

As ulipristal acetate is indicated for emergency contraception, no off-label use in prepubertal children is anticipated.

The measures described above for off-label use in adults apply to ulipristal acetate use in post-pubertal children.

SVI.7. Conclusions

Safety concerns from this module (to be carried through to Part II Module SVIII)	
Safety concern	Comment
No safety concern identified	NA

PART II MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

SVII.1. Newly identified safety concerns (since this module was last submitted)

There are no new identified safety concerns.

SVII.2. Recent study reports with implications for safety concerns

None

SVII.3. Details of important identified and potential risks from clinical development and post-authorisation experience (including newly identified)

No important identified risks as per GVP module V were mentioned for ellaOne in the previous EU RMP version.

No new important risk can be identified to be associated with switch to non-prescription status which is the subject for present application and the reason for this RMP update.

The following important potential risks are presented below: effects on pregnancy maintenance/off label use; risk of incomplete abortion and heavy bleeding; effects on foetus and newborns; ectopic pregnancy; concomitant use of CYP3A4 inducers; liver effect; delayed menstrual period> 60 days/amenorrhea and ovarian cysts.

In the previous approved RMP (version 12), the MAH had classified the safety concerns related to pregnancy reported after ellaOne intake into several important potential risks.

- The MAH considers that the risk of ectopic pregnancy is still to be considered as an important potential risk.
- With regards to the important potential risk "effects on pregnancy maintenance/off label use as abortifacient", the MAH proposes to reword it as "effects on pregnancy maintenance/off label use". The removal of the wording "as abortifacient" is proposed in line with the proposed risk minimisation activities, i.e. omission of any sentence suggesting that the product could be used to interrupt a pregnancy. Hence, the RMP includes a section accessible to the public and the MAH believes it would be important to avoid any such wording that may be misleading for women.
- The MAH has also proposed to improve the wording of an important potential risk: instead of "Unintended pregnancy exposure and the risk of incomplete abortion and heavy bleeding", this version of the RMP now reads "Risk of incomplete abortion and heavy bleeding" as this potential risk is not specific to unintended pregnancy exposure.
- With regards to the following important potential risks "*Effects in pregnancy in case of treatment failure*", "*Adverse pregnancy outcomes*" and "*Unintended pregnancy exposure (risk of malformation)"*, the MAH has taken into account the recommendation of the PRAC and will continue to monitor those risks through the risk management system as "important potential risks". However, considering that these three risks are all related to the effects of pregnancy exposure or treatment failure, and to avoid redundancies in the RMP, the MAH proposes to group them into "*Effects on foetus and newborn*". This potential risk, together

with the other potential risks in relation to pregnancy exposure, will cover the entire scope of potential adverse outcomes.

Preclinical data from pre- and post-natal development study in rats that assessed animal safety of ulipristal acetate when given to pregnant animals are available as mentioned in section SII. Ulipristal acetate administered to pregnant rats throughout gestation and up to weaning did not affect the physical development, learning capacities and performance in behavioral tests, as well as the sexual maturation, mating performance and fertility of the offspring.

Clinical and post-marketing data on 533 pregnancies (including 441 post-marketing cases) reported after ellaOne intake, do not suggest any effects on pregnancy outcome.There is no signal for a fetotoxic effect of ulipristal acetate, the observed anomalies having not been assessed as related to the drug.

The number of exposures during pregnancy (i.e. women were not aware that they were pregnant at the time of ellaOne intake) was 40 and the outcomes were as follows: two births of healthy babies, two spontaneous abortions, 20 elective terminations (including one therapeutic termination), two ongoing pregnancies and 14 cases with an unknown outcome or loss to follow-up.

Nevertheless, the MAH will continue monitoring all pregnancy reports and outcomes through routine pharmacovigilance and through the information collected via the web-based pregnancy registry and propose providing PSURs to the Agency on an annual basis after the reclassification for two years, including an update on pregnancy cases.

Potential risk: Effect on pregnancy maintenance / Off-label use	
Frequency with 95 % CI	Ulipristal acetate has never been intentionally administered to pregnant women and the available clinical body of evidence comes from inadvertent exposure of pregnant women or from women becoming pregnant despite ulipristal acetate intake (failure). The failure (pregnancy) rate observed in clinical efficacy studies is indicative that the product is not effective to interrupt a pregnancy. A single dose of 30 mg has also been used inadvertently by 11 pregnant women during clinical trials and such inadvertent exposure was also reported by at least 40 women since launch. In all cases, pregnancies continued normally and no adverse gynecological or obstetrical outcomes attributed to ulipristal acetate exposure have been reported. Occurrence of spontaneous miscarriage reported is similar to what occurs in the general population. In post-marketing surveillance, no hemorrhagic event or other relevant signal has been reported which could have suggested any possible incomplete miscarriage. This is in line with data from experimental animal models showing that the dose used for emergency contraception is not effective to induce fetal loss. The potential risk of off-label use was assessed through a survey among prescribers of six EU countries (FUM/MEA008). The results of the survey did not identify any signal of attempted use of ulipristal acetate 30 mg to terminate an established pregnancy. Off label use of ulipristal acetate 30 mg (either use outside the approved time window and/or use in a woman already pregnant) was observed in less than 1% of patients. The qualitative survey (interviews) and evaluation of patient cases did not suggest that ulipristal acetate 30 mg was prescribed off label as an abortifacient. Nevertheless, the relatively high percentages of prescription beyond 5 days in Poland and Sweden (Poland 31% (n=13) and in Sweden 34.5% (n=10)) resulted from the quantitative questionnaire was not explained. As the percentages were not in line with those reported for some other countries, it was suggested by the CHMP that sampling error might be the reason for such differences. The MAH

Potential risk: Effect on pregnancy maintenance / Off-label use	
	was requested to repeat the study in the two countries Poland and Sweden, with a new set of participating prescribers and to investigate the reasons for prescribing ulipristal acetate 30 mg off label. HRA Pharma repeated the questionnaire in Poland and Sweden utilizing a new sample of HCPs. The questionnaire was updated with questions that verify the reason for prescribing ulipristal acetate 30 mg off label. The repeat study (HRA2914-544a) did not show an increased rate of off label in Poland or Sweden. In both countries, 20% of prescribers recalled to have prescribed at least once ulipristal acetate 30 mg more than 5 days after the unprotected intercourse. This finding is in line with the percentages found in the other countries. These percentages are also in line with the percentages of physicians who reported at least once the prescription of levonorgestrel more than 3 days after the unprotected intercourse. The frequency of and reasons for these off label prescriptions have been assessed. When a prescriber indicated to have prescribed more than 5 days after UPI, this happened between 1 to 3 times. The main reason for prescription more than 5 days after UPI was the uncertainty about the date of the unprotected intercourse. Additional reasons that were clearly expressed are the fear of the women to become pregnant in combination with the idea that the product might still prevent a pregnancy even if taken more than 5 days after UPI. No off label prescriptions were reported to have any relationship with an intent to terminate an existing pregnancy. In comparison to results obtained for levonorgestrel, there was no indication of higher rate of off label use associated with ulipristal acetate 30 mg. In conclusion, the results of the survey (qualitative and quantitative phases) did not identify any signal of attempted use of ulipristal acetate 30 mg to terminate an ongoing pregnancy. Results of these studies were assessed by the PRAC who agreed that the data were satisfactory to fulfill this Post-Authorisation Commitment (PAC No. MEA/008.8 fulfilled by CHMP opinion dated 20/09/2013). No report of effect on pregnancy maintenance has been reported since the launch of ulipristal acetate 30 mg. One report of off label use has been reported since the launch of ulipristal acetate 30 mg, by a patient who took ellaOne on the day of pregnancy diagnosis via the pregnancy registry in [redacted]. No information was provided regarding the outcome of the pregnancy.
Seriousness/outcomes	Not known
Severity and nature of risk	Termination of pregnancy.
Background incidence/prevalence	Not applicable.
Risk groups or risk factors	Not applicable.
Potential mechanisms	Antagonism of progesterone action
Preventability	SPC and PL
Impact on individual patient	Pregnancy loss
Potential public health impact of safety concern	Minor to none
Evidence source	Post-marketing data HRA2914-544, 544a and HRA2914-542 (off label use survey)
MedDRA terms	Off label use (10053762)

Potential risk: Risk of incomplete abortion and heavy bleeding	
Frequency with 95 % CI	During clinical trials, among 92 pregnancies reported, no pregnancy ending with an incomplete abortion was reported and 15 ended with a spontaneous abortion. All miscarriages resolved spontaneously without further complication and none required an additional curettage. The rate of spontaneous abortion (16.3 %) is not higher than that in the general population. Bleeding was reported as an AE in only 4 instances as either 'mild' or 'spotting' 4 to 15 days after treatment, 2 pregnancies were then lost to follow-up and 2 went on to have an elective termination of their pregnancy. Since launch, among 441 pregnancies reported, no hemorrhagic event or other relevant signal could have suggested any possible incomplete miscarriage. Thirty (30) pregnancies which ended with a spontaneous abortion were reported, including 1 incomplete spontaneous abortion, 1 missed abortion and 2 cases of blighted ovum and 1case of blighted ovum ended with induced abortion were reported. The causal relationship between ulipristal acetate 30 mg and incomplete/missed abortion was not assessed. Experimental animal models showed that the dose used for emergency contraception is not effective to induce fetal loss. A comprehensive search for all cases of heavy bleeding received from launch to 14 May 2014 was performed in the PV database. In 69 cases, bleeding occurred in non-pregnant patients: 6 patients experienced heavy menstruation, 6 patients experienced heavy intermenstrual bleeding and 57 patients experienced mild or light vaginal bleeding. In 20 cases, bleeding occurred in pregnant patients: 1 patient experienced light bleeding an unspecified time after exposure to ellaOne during pregnancy, 8 patients experienced bleeding as first signs of spontaneous abortion or blighted ovum or ruptured of an ectopic pregnancy, 10 patients experienced bleeding during pregnancy, and 1 patient experienced vaginal bleeding after an induced abortion.
Seriousness/outcomes	Spontaneous and incomplete abortions may require a hospitalisation and curretage therefore would be a serious event. Patients usually recover without sequelle.
Severity and nature of risk	Spontaneous and incomplete abortion is usually of mild to moderate severity when timely medical care is provided.
Background incidence/prevalence	The overall miscarriage rate is reported as 15-20%, which means 15-20% of recognized pregnancies result in miscarriage. The frequency of spontaneous miscarriage increases further with maternal age. When pregnancy is systematically detected very early, the magnitude of pregnancy loss significantly increases to about 30% (Wilcox, 1988). Approximately 80% of miscarriages occur within the first trimester.
Risk groups or risk factors	Maternal age over 38 years
Potential mechanisms	Antagonism of progesterone action
Preventability	SPC and PL
Impact on individual patient	Need for standard treatment of incomplete abortion
Potential public health impact of safety concern	Minor to none
Evidence source	Post-marketing and clinical data
MedDRA terms	Abortion missed (10000230) Abortion spontaneous (10000234) Abortion spontaneous incomplete (10061617) Vaginal haemorrhage (10046910) Genital haemorrhage (10061178)

Potential risk: Risk of incomplete abortion and heavy bleeding	
	Menorrhagia (10027313) Metrorrhagia (10027514) Menometrorrhagia (10027295) Haemorrhages (10055798)

Potential risk: Effects on foetus and newborns	
Frequency with 95 % CI	All available body of evidence suggest that there is no risk of malformations due to UPA. Main evidence comes from a pre- and post-natal development study performed in rats, and assessing animal safety of UPA when given to pregnant animals. Ulipristal acetate administered at doses giving exposure in the same range as the human dose did not affect the physical development, learning capacities and performance in behavioural tests, as well as the sexual maturation, mating performance and fertility of the offspring. Of the 533 pregnancies (92 in clinical trials plus 441 post-marketing cases) that have been reported as ulipristal acetate 30 mg tablet failures or inadvertent exposures to UPA, no cases of malformations clearly related to ulipristal acetate 30 mg tablet treatment have been reported. In the clinical trial HRA2914-509 (identical to study -005), one of the infants presented with visual impairment diagnosed at 2 months of age, which was not considered secondary to treatment intake by investigators, and for which no aetiology has been identified by the caring physicians during work-up. An independent Data Safety Monitoring Board (consisting of three independent experts: a gynaecologist-obstetrician, a neonatologist and an endocrinologist) reviewed the case and confirmed that optic nerve atrophy is a well-known neonatal syndrome and a leading cause of infant blindness in many countries for which only two risk factors have been identified, the young age and primiparity of the mother. The Board also stated that none of the drugs taken by the mother during pregnancy (pseudoephedrine, thyroid hormones, or the drug under study) are known to be associated with this syndrome. The Board unanimously concluded that the link between this neonatal outcome and the study drug was unlikely. Since launch, one case of trisomy 21 was collected and was considered as unlikely-related to ulipristal acetate 30 mg tablet by HRA Pharma, considering the date of administration and the chronology of the reaction. This 42-year old patient was at 6 weeks and 2 days of amenorrhea when she took ulipristal acetate 30 mg and underwent a therapeutic pregnancy termination at 17 weeks and 5 days of amenorrhea further to a diagnosis of trisomy 21 (confirmed by a trophoblast biopsy). One case of foetal cardiac defect discovered at 12 weeks of pregnancy was received from health authorities. It concerned a 18-year old woman who experienced vaginal spotting fourteen days after ulipristal acetate 30 mg intake and starting of desogestrel/ethinylestradiol. A pregnancy termination was performed at 13 weeks. The relationship to the drug was assessed as uncertain by the reporter. No further information has been received despite several follow up requests. One report of neonatal hypoxic ischaemic encephalopathy occurred at 40 weeks and 3 days of gestation in an otherwise uneventful pregnancy. The baby was in occiput position at the time of delivery and a C-section was performed due to foetal distress. The infant suffered from hypoxic ischemic encephalopathy, left epidural haematoma and multiple parenchymal haematomas. A causal relationship between this complication of delivery and ellaOne intake more than 8 months

Potential risk: Effects on foetus and newborns	
	prior is unlikely as this adverse foetal outcome is the consequence of a delivery complication and associated neonatal distress.All available body of evidence suggest that there is no adverse pregnancy outcome. A 30-year old mother with a history of one previous [redacted] with no alcohol, cigarettes or illicit drugs addiction, was pregnant after ellaOne intake 17 days after LMP for post-coital contraception. The mother experienced pre-term premature rupture of membranes in week 31+2. The infant at birth weighed 2320 g, length 49 cm. Hypoglycemia after birth, macroglossia, small umbilical hernia, diastases recti, large-for-age, nephromegaly and muscular hypotonia led to the diagnosis of a Beckwith-Wiedemann syndrome, which was confirmed by molecular genetic analysis. The development of the child was delayed. The baby was also exposed in utero to enoxaparin 80 mg for mother's pelvic venous thrombosis from gestational week 24 to birth, and folic acid for prophylaxis of neural tube defect, from gestational week 6 to birth. A causal relationship between the reaction and ellaOne cannot be formally excluded; however, no similar reports were received and considering the available data, no medical conclusion can be drawn. One case of diaphragmatic aplasia and fetal cardiopathy was reported by a gynecologist. A 39-year old woman, with two normal previous pregnancies, was pregnant following ellaOne intake, 24 hours after unprotected intercourse, and 15 days after LMP. The woman was not pregnant at time of ellaOne intake. On pregnancy week 22, a level two ultrasound revealed diaphragmatic aplasia and cardiopathy of the foetus, leading to an [redacted] The woman was concomitantly treated with diclofenac, taken occasionally during pregnancy as anti-inflammatory, ferrous and folic acid (dose, indication and time of exposure not specified). The data do not allow performing an accurate causality assessment. Therefore, this case is considered as not assessable.
Seriousness/outcomes	Not applicable: theoretical risk.
Severity and nature of risk	Not applicable: theoretical risk.
Background incidence/prevalence	Not available for effects on pregnancy With regards to effects on foetus and newborns, congenital anomalies are reported in some 2.2% of live births, with the most common anomalies being cardiac malformations (68/10,000 births), orofacial clefts (16/10,000 births) and genital malformations (16/10,000 births) (EUROCAT Central Registry, Report 2004-2005).
Risk groups or risk factors	Some congenital anomalies can be attributed to a mother's genetic predisposition. Other risk factors include age (over 35), use of certain drugs and alcohol, and smoking during pregnancy. Oral contraception (OC) exposure in early pregnancy has not been shown to increase the risk of congenital malformations. Mothers of 9,986 infants with 32 types of birth defects and 4,000 infants without birth defects were included in the multisite, case-control, National Birth Defects Prevention Study. (Waller, 2010) Maternal OC use during the first 3 months of pregnancy was associated with an increased odds ratio for 2 of 32 birth defects: hypoplastic left heart syndrome (adjusted odds ratio =2.3 [95% confidence interval=1.3-4.3) and gastroschisis (1.8 [1.3-2.7]). Results of this study should be interpreted as hypotheses until they can be evaluated further. Overall, this study is consistent with findings of previous studies that administration of OC during early pregnancy is not associated with increased rate of congenital malformation in offspring (Waller, 2010).
Potential mechanisms	None
Preventability	SPC and PL

Potential risk: Effects on foetus and newborns	
Impact on individual patient	Burden of treatment / care
Potential public health impact of safety concern	Significant potential public health risk is unlikely.
Evidence source	Literature eCTD Clinical and Non-clinical Overviews Post-marketing data
MedDRA terms	Unintended pregnancy (10045542) SOC Congenital, familiar and genetic disorders (100110331)

Potential risk: Risk of ectopic pregnancy	
Frequency with 95 % CI	Progesterone receptors modulators have no effect on tubular motility (Gazvani 1998, Gemzell 2004). Therefore there is no reason to anticipate more ectopic pregnancies in case of treatment failure During the clinical studies with ulipristal acetate, no ectopic pregnancy was observed. As of 14 May 2014, 441 pregnancies were reported to be exposed to ulipristal acetate and so far 10 cases of ectopic pregnancy have been reported. Vaginal bleeding was reported in 2 cases. The patient recovered in 8 cases wheras the outcome was not provided in the remaining 2 cases.
Seriousness/outcomes	Ectopic pregnancy is a life-threatening event, especially without a timely medical care. Ectopic pregnancies are responsible for 4.9% of all maternal deaths in developed countries and 0.1-0.5% in developing countries (Khan *et al*, 2006).
Severity and nature of risk	Ectopic pregnancy may be moderate to severe, depending on the individual conditions of the patient and the availability of appropriate treatment.
Background incidence/prevalence	The incidence of ectopic pregnancy has been reported to be approximately 1/1000 women 15-44 per year or 20/1000 pregnancies per year (Van den Eeden *et al*, 2005; Coste *et al*, 2004; Tay *et al*, 2000).
Risk groups or risk factors	The risk of ectopic pregnancy increases with age and number of sexual partners as well as history of ectopic pregnancy, pelvic infection, infertility, cigarette smoking, prior cesarean section, pelvic surgery or tubal surgery (Karaer *et al*, 2006; Menon *et al*, 2007; Bouyer, 2003). Progestin-only pills administered continuously lower the absolute rate of ectopic pregnancy; however, if pregnancy does occur, the chance that it will be ectopic is increased threefold (Corcoran *et al*, 1977). The suspected mechanism of action is progestin effects on tubal motility. Indeed, high levels of progesterone may cause ciliary dysfunction and may be a possible cause of ectopic pregnancy (Paltieli *et al*, 2000).
Potential mechanisms	Progesterone receptor modulators have no effect on tubular motility (Gazvani 1998, Gemzell 2004).
Preventability	Product information
Impact on individual patient	Risk of severe complications
Potential public health impact of safety concern	Significant potential public health risk is unlikely
Evidence source	Literature eCTD Clinical and non clinical overviews.
MedDRA terms	Ectopic pregnancy (10014166) Tubal rupture (10067553) Abortion of ectopic pregnancy (10066266) Ruptured ectopic pregnancy (10048407)

Potential risk: Liver effects	
Frequency with 95 % CI	An increase in liver weight associated with hepatocyte hypertrophy was found in the repeated dose toxicity study performed in rats; that was interpreted as an adaptative mechanism. In addition liver enzymes in this species, were either decreased (ALT) or not modified (GGT, AST). Abnormal liver function tests have not been reported as adverse events during the clinical trials. In the studies where liver function has been assessed (HRA 2914-503, HRA 2914-504, HRA 2914-505, HRA 2914-510, HRA 2914-509), no significant abnormality has been observed except in one subject (HRA 2914-509) with normal screening hepatic panel who was found to have an isolated and moderate increase in ALT (74/N below 55) and in AST (88/N below 45) 12 days after treatment. Repeat enrollers in the phase III program had no abnormal liver function results. In the only chronic dose study sponsored by HRA Pharma (twelve weeks of daily dosing in healthy women volunteers), HRA2914-510, liver function tests showed no variation between baseline and after 3 months of treatment at 2.5, 5 or 10 mg ulipristal acetate daily. In the lactation study (HRA2914-514) AST and ALT parameters were abnormal for one subject, not clinically significant at the screening visit (34 and 71 U/L, respectively), and at the end of study visit, these values had increased to 90 and 153 U/L, respectively and were abnormal, clinically significant. None of these parameters were reported as AEs. ALP values were abnormal, considered as not clinical significant both at the screening visit and end of visit. Total bilirubin values were normal: respectively 0.24 mg/dL and 0.21 mg/dL at the screening and end of study visits and GGT values were normal at both visits at 26 U/L and 33 U/L, respectively. No signal was observed in post-marketing surveillance. One case of late increased Gamma GT reported and assessed as unlikely related to ellaOne intake by HRA Pharma was collected since the launch of ellaOne (see PSUR 3). Clinically relevant elevations in liver enzymes have been noted in studies with SPRM such as telapristone acetate and onapristone (Robertson *et al*, 1999) but not with other SPRMs including ulipristal acetate, asoprisnil (Chwalisz *et al*, 2007) and mifepristone (Carbonell *et al*., 2008), suggesting that this effect may be specific to telapristone acetate and onapristone rather than being a class effect.
Seriousness/outcomes	Non-serious rare laboratory finding.
Severity and nature of risk	The laboratory observations were mild.
Background incidence/prevalence	Prevalence of ALT elevation above the ULN is 3 to 15% in the general population.
Risk groups or risk factors	None identified
Potential mechanisms	Not known.
Preventability	Not applicable.
Impact on individual patient	No impact expected
Potential public health impact of safety concern	No public health risk expected.
Evidence source	PSUR 3; study report of lactation study (HRA2914-514)

Potential risk: Liver effects	
MedDRA terms	Gamma-glutamyltransferase increased (10017693)

Potential risk: Delayed menstrual period > 60 days / amenorrhoea	
Frequency with 95 % CI	During phase III clinical trials, 0.3 % (8 out of 2,488) of women experienced a delay of more than 60 days beyond the anticipated onset of menses which was clinically considered as amenorrhoea. None were pregnant. One case of delayed menstrual period > 60 days and 3 cases of amenorrhoea with outcome not reported have been reported since the launch of ellaOne.
Seriousness/outcomes	If we exclude a pregnancy, this risk is considered as non serious.
Severity and nature of risk	Not applicable: the severity of amenorrhea depends on its etiology and is therefore non-severe if related to ulipristal acetate intake. (see above).
Background incidence/prevalence	The most common cause of amenorrhea is pregnancy. If amenorrhea due to pregnancy is excluded, the prevalence among women of reproductive age is approximately 3%.
Risk groups or risk factors	Stress is a known risk factor and is likely a contributing factor to women seeking to avoid an unplanned pregnancy. Additionally, athletes, and women with endocrine or eating disorders are at increased risk for developing amenorrhea.
Potential mechanisms	Mechanism is unknown or related to stress and anxiety linked to pregnancy risk
Preventability	Product information
Potential public health impact of safety concern	Significant potential public health risk is unlikely.
Evidence source	Module 5, study reports HRA 2914-509 and HRA 2914-513 Pettersson F, Fries H, Nillius SJ. Epidemiology of secondary amenorrhea. Incidence and prevalence rates. Am J Obstet Gynecol. 1973; 117 (1): 80-6. Warren MP. Clinical review 77: evaluation of secondary amenorrhea. J Clin Endorinol Metab. 1996; 81(2): 437-42.
MedDRA terms	Amenorrhoea (10001928) Menstruation delayed (10027336)

Potential risk: Ovarian cysts	
Frequency with 95 % CI	Systematic ultrasonographic examinations were performed in all four pharmacodynamic studies to document follicular development. In three such studies, ovarian cysts were observed: a) In study HRA 2914-505 asymptomatic cysts (diameter 15 to 33 mm) were observed in 10 women in three groups (10, 50 and 100 mg ulipristal acetate and placebo). They resolved within two months in 9 cases whereas in the 10th subject, a 16-mm cyst persisted at 3-month follow-up, she had received a single 100-mg dose of ulipristal acetate. One woman had a ruptured cyst during follow-up, she had received a single 10-mg dose of ulipristal acetate. b) In study HRA 2914-506, twelve women from all doses (placebo, 10, 50 or 100 mg single dose) had ovarian cysts between 15 and 20 mm in diameter at the time of endometrial biopsy. None were present by the end of the post-treatment cycle. In this study, if an echogenic ovarian structure measuring more than 15 mm was noted on luteal phase vaginal sonography, a "presumed cyst" was diagnosed. At the time of biopsy, ten of the 56 women from all

Potential risk: Ovarian cysts	
	dose groups (n = 3 placebo, 4 at 10 mg, 2 at 50 mg, 1 at 100 mg) had presumed cysts between 12 and 24 mm in maximum diameter. The number of women is not sufficient to exclude a dose effect or an effect of the drug at all. However, based on these small numbers, there is no clear indication that the presumed cysts are related to ulipristal acetate or its dose, since 3 placebo women had them and only 1 in the 100 mg group. c) In study HRA 2914-510 of twelve weeks continuous daily dosing, a total of 21 ovarian cysts were reported in 18 subjects in all four groups (2.5, 5 and 10mg daily and the placebo groups) during the treatment phase. All spontaneously resolved after the end of the treatment except for one in the 5 mg group which subsequently led to ovariectomy nearly 2 years after the stopping the study treatment. The pathology report showed multiple functional cysts and one calcified benign cystadenoma. No ovarian cyst led to study discontinuation. In the phase II studies, ovarian cysts were also reported by subjects: - In the study HRA 2914-507, the only ovarian cyst reported was in the levonorgestrel group. - In the study HRA 2914-508, ovarian cysts were observed in both groups (50mg and 10mg) with equal frequency. In the phase III studies, ovarian cyst rupture was reported only in one subject (HRA 2914-509) as an adverse event and spontaneously resolved. Ovarian cysts have been noted in both ulipristal acetate and placebo groups at systematic ultrasound search; - All but one resolved spontaneously during the treatment cycle or within 3 months. One single case lead to ovariectomy 2 years after study completion: the pathology report showed a calcified benign cystadenoma. - All but one resolved spontaneously during the treatment cycle or within 3 months. One single case lead to ovariectomy 2 years after study completion: the pathology report showed a calcified benign cystadenoma. - The occurrence of functional cysts is frequent with any medication interfering with the pituitary-ovarian axis as contraceptives (combined, progestin-only and IUD): cyst frequency goes from 1 to 20% with combined pills, more than 25% with progestin implants, more than 60% in women taking progestin-only pills (Broome et al, 1995; Egarter et al 1995; Hidalgo et al, 2006; Alvarez-Sanchez, 2000). Functional cysts develop from unruptured follicles growing under unsuppressed pituitary FSH and LH, they usually disappear after the next menses with dropping pituitary hormones or after the end of contraceptive treatment. As with other contraceptives, because LH peak is stunted with ulipristal acetate, the follicles which are not ovulated may continue to grow leading to similar spontaneously regressive functional cysts. The occurrence of "ruptured ovarian cysts" is mentioned in the SmPC as a rare adverse event in section 4.8. A search was performed in the PV database for all post-marketing cases of

Potential risk: Ovarian cysts	
	ovarian cysts. Three (3) cases of ovarian cyst have been reported since the launch of ellaOne to 14 May 2014. In all 3 cases, no medical conclusion could be drawn on ellaOne causal role in the occurrence of the ovarian cyst.
Seriousness/outcomes	Most ovarian functional cysts found incidentally do not require treatment. They usually disappear on their own within 60 days. The seriousness is also depending on the size of the cyst and how it appears on the ultrasound and the potential risk of complication.
Severity and nature of risk	See above
Background incidence/prevalence	Ovarian cysts occur in 30% of females with regular menses, 50% of females with irregular menses (Duklewski).
Risk groups or risk factors	No known risk factors for development of ovarian cysts among reproductive aged women have been identified.
Potential mechanisms	Ulipristal acetate, like other steroidal contraceptives, blunts the LH surge, thereby allowing for the development of functional ovarian cyst.
Preventability	Product information
Potential public health impact of safety concern	Unlikely to have a significant public health impact
Evidence source	Duklewski, Kimberly, and Andrew Aronson. "Ovarian Cysts." *eMedicine*. Eds. Dana A. Stearns, et al. 18 Jun. 2007. Medscape. 28 Jul. 2009
MedDRA terms	Ovarian cyst (10033132) Cyst (10011732) Ovarian cyst ruptured (10033136)

SVII.4. Identified and potential interactions

SVII.4.1 Overview of potential for interactions

Due to the single dose regime, potential for serious consequences of interactions is considered low.

SVII.4.2 Important identified and potential interactions

The following interactions are discussed below: effects of concomitant use with CYP3A4 inducers, effects of concomitant use of progestin only contraception.

Interacting substances	CYP3A4 Inducers
Effect of interaction	Data from a drug-drug interaction study show that the administration of ulipristal acetate with a strong CYP3A4 inducer such as rifampicin markedly decreases C_{max} and AUC of ulipristal acetate by 90% or more and decreases ulipristal acetate half-life by 2.2-fold corresponding to an approximately 10-fold decrease of ulipristal acetate exposure. Concomitant use of ellaOne with CYP3A4 inducers (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, efavirenz, fosphenytoine, nevirapine, oxcarbazepine, primidone, rifabutine, St John's wort/*Hypericum perforatum*) therefore reduces plasma concentrations of ulipristal acetate and may result in a decreased efficacy of ellaOne and is therefore not recommended.

Interacting substances	CYP3A4 Inducers
	A search performed in the pharmacovigilance database retrieved one non-serious case of concomitant use of ulipristal acetate 30 mg tablet and *Hypericum perforatum* (St John's wort). The woman experienced delayed menstruation. Serum drug levels and outcome were not provided. No interaction between ulipristal acetate and St John's wort was suspected.
Evidence source	Module 2.7.2 Spontaneous reports and studies HRA2914-430 & HRA2914-551
Possible mechanisms	Ulipristal acetate is metabolized by CYP3A4 enzyme in human liver microsomes in vitro. Co-administration with potent CYP3A4 inducers (e.g., rifampicin, phenytoin, phenobarbital carbamazepin, St John's wort) may reduce plasma concentration of ulipristal acetate and may result in a decrease in efficacy.
Potential health risk	Interaction may lead to lack of efficacy of ulipristal acetate (pregnancy).
Discussion	The results of the Drug-Drug Interaction study with rifampicin (HRA2914-551) were submitted in a variation and the product information has been modified accordingly.

Interacting substances	Products interacting with the progesterone receptor
Effect of interaction	Since launch and up to 14 May 2014, a total of 13 pregnancy cases in which a concomitant use of progestin-only hormonal contraceptive with ellaOne were reported. Among these cases, 4 cases were associated with a possible or confirmed EC lack of efficacy. The 4 cases also corresponded to a quickstart of the hormonal contraception on the day of ellaOne intake. A total of 35 pregnancy cases in which concomitant use of combined estro-progestin hormonal contraceptives with ellaOne was reported. Among these 35 cases, 16 were reported together with a case of pregnancy compatible with a lack of efficacy of ellaOne. Of those 16 cases, 13 corresponded to the initiation (quickstart) of a regular hormonal contraception on the day of ellaOne intake and 2 corresponded to the use of ellaOne because pills of an ongoing regular combined contraception were missed.
Evidence source	Spontaneous reports
Possible mechanisms	Ulipristal acetate is a progesterone receptor modulator with antagonistic activities. Because ulipristal acetate binds the progesterone receptor with high affinity, it may in theory interfere with the action of progestin-only contraceptives (including levonorgestrel emergency contraception).
Potential health risk	Interaction may lead to lack of efficacy of ulipristal acetate (pregnancy).
Discussion	The effect of concomitant use of progestin-only contraception is included as missing information in this RMP.

SVII.5. Pharmacological class effects

Ulipristal acetate belongs to the selective progesterone receptor modulator class and therefore exerts both agonist and antagonist progesterone activities in a cell-specific manner. When used in emergency contraception (at doses of 10-25 mg), the safety profile of mifepristone is comparable to the safety profile of ulipristal acetate (von Hertzen et al, 2002).

Ulipristal acetate may also display anti-glucocorticoid activity, but to a lesser extent than that exerted by mifepristone.The anti-glucocorticoid activity of the latter, evidenced by an ACTH elevation, has not been observed at the dose of 200mg/d for several years (157 months)

(Grunberg et al. 2006).Therefore, at the dose recommended for emergency contraception (30 mg single use), ulipristal acetate is not expected to have anti-glucocorticoid activity.

Indeed, although toxicology studies suggest antiglucocorticoid effects of ulipristal acetate, in humans no antiglucocorticoid effect (evidenced by an increase in ACTH and/or cortisol) has been observed with single doses up to 200 mg (study HRA2914-503) or with repeat administration of ulipristal acetate at the daily dose of 10 mg orally for 3 months (study HRA2914-510).

SVII.5.1 Pharmacological class risks already included as important identified or potential risks

No pharmacological class effects were included in the important safety concerns.

SVII.5.2 Important pharmacological class effects not discussed above

Not applicable.

PART II MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

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

PART III PHARMACOVIGILANCE PLAN

III.1 Safety concerns and overview of planned pharmacovigilance actions

Important identified risks

None.

Important potential risks

Effect on pregnancy maintenance / off-label use		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Level of risk, risk factors	Routine pharmacovigilance	
	Use of specific report form for spontaneous report	Better characterize the event, the surrounding circumstances, the outcome; ensure complete data capture for improving causality assessment.
	Special attention in PSURs	Assess cumulative information on risks and benefits
	Web based pregnancy registry with online questionnaire and access to HCPs and women	Assess clinical follow-up and outcome of pregnancies resulting from ulipristal acetate 30 mg /ella failure or pregnancies inadvertently exposed to ulipristal acetate 30 mg ella. Improve follow-up and outcome of pregnancy reports

Risk of incomplete abortion and heavy bleeding		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Level of risk, risk factors	Routine pharmacovigilance	To monitor for a change in the nature, severity, or frequency of these events.
	Use of specific report form for spontaneous report	Better characterize the event, the surrounding circumstances, the outcome; ensure complete data capture for improving causality assessment.
	Special attention in PSURs	Assess cumulative information on risks and benefits
	Web based pregnancy registry with online questionnaire and access to HCPs and women	Assess clinical follow-up and outcome of pregnancies resulting from ulipristal acetate 30 mg failure or pregnancies inadvertently exposed to ulipristal acetate 30 mg. Improve follow-up and outcome of pregnancy reports

Effects on foetus and newborns		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Risk factors, level of risk	Routine pharmacovigilance	Follow-up of all exposed pregnancies
	Special attention in PSURs	Provide cumulative analysis and assess benefit risk balance
	Use of specific pregnancy report form for spontaneous report	Better characterize the event, the surrounding circumstances, and the outcome; ensure complete data capture for improving causality assessment.
	Web based pregnancy registry with online questionnaire and access to HCPs and women	Assess clinical follow-up and outcome of pregnancies resulting from ellaOne failure or pregnancies inadvertently exposed to ellaOne. Improve follow-up and outcome of pregnancy reports

Risk of ectopic pregnancy		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Level of risk, Risk factors	Routine pharmacovigilance	Detect early any risk factors, and collect maximum information on reported suspected ADRs.
	Use of specific pregnancy report form for spontaneous report	Better characterize the event, the surrounding circumstances, the outcome; ensure complete data capture for improving causality assessment.
	Special attention in PSURs	Special attention on ectopic pregnancies reported as such and on reports of abdominal pain that may be a sign of ectopic pregnancy Provide cumulative review using all available information and assess benefit-risk balance
	Web based pregnancy registry with online questionnaire and access to HCPs and women - ongoing	Assess clinical follow-up and outcome of pregnancies resulting from ellaOne failure or pregnancies inadvertently exposed to ellaOne. Improve follow-up and outcome of pregnancy reports

Liver effects		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Level of risks	- Routine pharmacovigilance - Use of specific liver report form for spontaneous report	Better characterize the risk of hepatic effect in terms of description, severity, outcome, risk factors.

	- Special attention in PSURs	The specific form provides a support for follow up of cases reported by health professionals and ensures complete data capture for improving causality assessment.

Concomitant use of CYP3A4 inducers		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Clinical significance of the interaction	Routine pharmacovigilance	Detect early any risk factors, and collect maximum information on reported suspected ADRs.

Delayed menstrual period >60 days / amenorrhea		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Level of risks	- Routine pharmacovigilance - Special attention in PSURs	Detect early any risk factors, and collect maximum information on reported suspected ADRs

Ovarian cysts		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Risk factors, level of risk	- Routine pharmacovigilance - Special attention in PSURs	Detect early any risk factors, and collect maximum information on reported suspected ADRs

Missing information

Effect of concomitant use of progestin-only contraception		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Clinical significance of the interaction	Routine pharmacovigilance	Detect early any risk factors, and collect maximum information on reported suspected ADRs

Effect in women with severe asthma treated by oral glucocorticoid		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Clinical significance of the interaction	Routine pharmacovigilance	Detect early any risk factors, and collect maximum information on reported suspected ADRs

Effects in women with impaired liver function		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Clinical significance of impaired liver function effect on ellaOne clinical effects	Routine pharmacovigilance	Detect early any risk factors, and collect maximum information on reported suspected ADRs

III.2 Additional pharmacovigilance activities to assess effectiveness of risk minimisation measures

No additional pharmacovigilance activities are planned.

III.3 Studies and other activities completed since last update of Pharmacovigilance Plan

Study/activity title **Observational study to assess safety in women < 18 years** (HRA2914-515)	
Safety concern(s)/risk minimisation measure investigated	Effect on pregnancy maintenance / off-label use Risk of incomplete abortion and heavy bleeding Effects on foetus and newborns Risk of ectopic pregnancy Effect in post pubertal children
Brief summary of results	The results of this study did not bring to light any new adverse events in the use of ella®/ellaOne® in routine conditions of use nor any clinically significant differences in the safety, tolerability or efficacy profile of ella®/ellaOne® between adolescents and adult women
Implications	Based on the results of this study (safety analysis performed on 579 women, of whose 279 being under 18 years), the MAH considers that "effect in post pubertal children" is no more a missing information.

III.4 Details of outstanding additional pharmacovigilance activities

Actions	**Milestone/exposure**	**Milestone/calendar time**	**Study status**
Registry of exposed pregnancies*	Based on voluntary reports through a website	Concomitantly with commercialization	Implemented Total of 41 pregnancy reports received via the registry since launch
Clinical follow-up of pregnancies in the practice of 1000 targeted prescribers*(HRA2914-012)	1000 targeted prescribers	First Site initiation June 2011- Final report planned Q4 2013	207 sites initiated 8 enrolled Study was stopped in 2013 and replaced by web-based pregnancy registry

III.4.1 Imposed mandatory additional pharmacovigilance activity (key to benefit risk)

None

III.4.2 Mandatory additional PhV Activity (being a Specific Obligation)

None

III.4.3 Required additional pharmacovigilance activities to address specific safety concerns or to measure effectiveness of risk minimisation measures

	Description of activity (or study title if known)	Milestone(s)	Due Date(s)
3	Registry of exposed pregnancies	PSUR evaluation	PSUR

III.4.4 Stated additional pharmacovigilance activities

None.

III.5 Summary of the Pharmacovigilance Plan

III.5.1 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and 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 Category: 3	To assess clinical follow-up and outcome of pregnancies resulting from ellaOnefailure 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.

III.5.2 Table of completed studies/activities from the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (Completed)	Date for submission of final study report
Prospective Observational Open-Label Multicenter Study to Assess the Safety, Tolerability and Efficacy of ellaOne (Ulipristal acetate) for Emergency Contraception in Postmenarcheal Adolescents and Adult Women International multicenter observationalstudy Protocol HRA2914-515 Category: 3	**Primary Objective**: To assess the safety and tolerability of ellaOne® in routine conditions of use for emergency contraception in postmenarcheal adolescents and adult women in particular menorraghia, metrorrhagia, dysmenorrhea and effect on menstrual cycles. **Secondary Objectives:** To assess the pregnancy rate observed after taking ellaOne® in routine conditions in postmenarcheal adolescents and adult women. To follow-up pregnant women throughout the pregnancy (check of potential complications) including fetal and neonatal follow-up. Number and percentage of patients with treatment emergent adverse events, regardless of relationship to study treatment and sorted by body system and preferred term will be summarized overall and for each subgroup of interest Additional safety parameters include menorraghia, metrorrhagia, dysmenorrhea and effect on menstrual cycles.	Effect in post pubertal children Effects on pregnancy maintenance / off-label use Risk of incomplete abortion and heavy bleeding Risk of ectopic pregnancy Effects on foetus and newborn	Completed	Final study report completed June 2013

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

IV.1 Applicability of efficacy to all patients in the target population

Target population in clinical trials support the indication of ellaOne: Emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure. The clinical trial population is a representative sample of population in clinical practice.

IV.2 Tables of post-authorisation efficacy studies

There are no post-authorisation efficacy studies planned as part of this RMP.

IV.3 Summary of post authorisation efficacy development plan

Not applicable.

IV.4 Summary of completed Post authorisation efficacy studies

Not applicable.

PART V RISK MINIMISATION MEASURES

V.1 Risk minimisation measures by safety concern

Safety concern	Effect on pregnancy maintenance / Off-label use
Objective(s) of the risk minimisation measures	Prevent use in pregnant women.
Routine risk minimisation measures	Text in SPC and package leaflet **SPC** **Section 4.2- Posology and method of administration** If a woman's menstrual period is late or in case of symptoms of pregnancy, pregnancy should be excluded before ellaOne is administered. **Section 4.4 –Special warnings and precautions for use** ellaOne does not prevent pregnancy in every case ellaOne inhibits or postpones ovulation (see section 5.1). If ovulation has already occurred, ellaOne is no longer effective. The timing of ovulation cannot be predicted and therefore ellaOne should be taken as soon as possible after unprotected intercourse. No data are available on the efficacy of ellaOne when taken more than 120 hours (5 days) after unprotected intercourse. Limited and inconclusive data suggest that there may be reduced efficacy of ellaOne with increasing body weight or body mass index (BMI) (see section 5.1). In all women, emergency contraception should be taken as soon as possible after unprotected intercourse, regardless of the woman's body weight or BMI. Women who become pregnant after taking ellaOne should contact their doctor (see section 4.6). If the next menstrual period is more than 7 days late, if the menstrual period is abnormal in character or if there are symptoms suggestive of pregnancy or in case of doubt, a pregnancy test should be performed. As with any pregnancy, the possibility of an ectopic pregnancy should be considered. It is important to know that the occurrence of uterine bleeding does not rule out ectopic pregnancy. **Section 4.6 – Fertility, pregnancy and lactation** Pregnancy ellaOne is not intended for use during pregnancy and should not be taken by any woman suspected or known to be pregnant (see sections 4.2). ellaOne does not interrupt an existing pregnancy. 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. Avoid language in SmPC and PL that could be misunderstood that ellaOne could be used to interrupt a pregnancy. **Package leaflet** **1.What ellaOne is and what it is used for**

Safety concern	**Effect on pregnancy maintenance / Off-label use**
	ellaOne does not work if you are already pregnant. If your menstrual period is late, there is a possibility that you may be pregnant. When your period is late or when you have symptoms of pregnancy (heavy breasts, morning sickness) you should consult a doctor or other healthcare professional before taking ellaOne. […] ellaOne is a contraceptive used to prevent a pregnancy from starting. If you are already pregnant it will not interrupt an existing pregnancy. **2. What you need to know before you use ellaOne** **Warning and precautions** Talk to your pharmacist, doctor or other healthcare professional before taking ellaOne • if your period is late or you have symptoms of pregnancy (heavy breasts, morning sickness), as you may already be pregnant (see section "Pregnancy, breast-feeding and fertility*")*; **Pregnancy, breast-feeding and fertility** *Pregnancy* Before taking ellaOne, if your period is late, tell your pharmacist, doctor or other healthcare professional, or do a pregnancy test in order to make sure you are not already pregnant (see section "Warning and precautions"). ellaOne is a contraceptive used to prevent a pregnancy from starting. If you are already pregnant it will not interrupt an existing pregnancy. If you become pregnant despite taking ellaOne, there is no evidence that ellaOne will affect your pregnancy. However, it is important that you see your doctor. As for any pregnancy, your doctor may want to check that the pregnancy is not outside the womb. This is especially important if you have severe abdominal (stomach) pain or bleeding or if you have previously had a pregnancy outside the womb, tubal surgery or long term (chronic) genital infection. If you become pregnant despite taking ellaOne, you are encouraged to ask your doctor to register your pregnancy in an official registry. You can also report this information on your own at www.hra-pregnancy-registry.com.Your information will remain anonymous – nobody will know it is information about you. Sharing your information may help women in the future understand the safety or risks of ellaOne during a pregnancy.
	Comment (e.g. on any differences between SmPCs) Not applicable.
	Other routine risk minimisation measures Not applicable.
Additional risk minimisation measure(s) (repeat as necessary)	Objective and justification of why needed
	Proposed actions/components and rationale
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Effectiveness will be measured by means of routine pharmacovigilance activities.
Criteria for judging the success of the proposed risk minimisation measures	Comparison of product information versus ICSRs.
Planned dates for assessment	Assessment will be performed during medical review of ICSRs and in PSUR.
Results of effectiveness measurement	Results will be presented regularly in PSUR and RMP updates.
Impact of risk minimisation	Minimisation of occurrence of the risk of off label use.

Safety concern	**Effect on pregnancy maintenance / Off-label use**
Comment	None

Safety concern	**Risk of incomplete abortion and heavy bleeding**
Objective(s) of the risk minimisation measures	Prevent use by already pregnant women
Routine risk minimisation measures	Text in SPC and package leaflet **SPC** **Section 4.2 - Posology and method of administration** If a woman's menstrual period is late or in case of symptoms of pregnancy, pregnancy should be excluded before ellaOne is administered. **Section 4.4 – Special warnings and precautions for use** If the next menstrual period is more than 7 days late, if the menstrual period is abnormal in character or if there are symptoms suggestive of pregnancy or in case of doubt, a pregnancy test should be performed. **Package leaflet** **Pregnancy, breast-feeding and fertility** If you become pregnant despite taking ellaOne, there is no evidence that ellaOne will affect your pregnancy. However, it is important that you see your doctor. As for any pregnancy, your doctor may want to check that the pregnancy is not outside the womb. This is especially important if you have severe abdominal (stomach) pain or bleeding or if you have previously had a pregnancy outside the womb, tubal surgery or long term (chronic) genital infection.
	Comment (e.g. on any differences between SmPCs) Not applicable.
	Other routine risk minimisation measures Not applicable.
Additional risk minimisation measure(s) (repeat as necessary)	Objective and justification of why needed
	Proposed actions/components and rationale
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Effectiveness will be measured by means of routine pharmacovigilance activities.
Criteria for judging the success of the proposed risk minimisation measures	Comparison of product information versus ICSRs.
Planned dates for assessment	Assessment will be performed during medical review of ICSRs and in PSUR.
Results of effectiveness measurement	Results will be presented regularly in PSUR and RMP updates.
Impact of risk minimisation	Minimisation of the occurrence of the use by pregnant women.
Comment	None

Safety concern	**Effects on foetus and newborn**
Objective(s) of the risk minimisation measures	To avoid use by pregnant women
Routine risk minimisation measures	Text in SPC and package leaflet **SPC** **Section 4.2 - Posology and method of administration**

Safety concern	Effects on foetus and newborn
	If a woman's menstrual period is late or in case of symptoms of pregnancy, pregnancy should be excluded before ellaOne is administered. **Section 4.4 –Special warnings and precautions for use** ellaOne does not prevent pregnancy in every case ellaOne inhibits or postpones ovulation (see section 5.1). If ovulation has already occurred, ellaOne is no longer effective. The timing of ovulation cannot be predicted and therefore ellaOne should be taken as soon as possible after unprotected intercourse. No data are available on the efficacy of ellaOne when taken more than 120 hours (5 days) after unprotected intercourse. […] Women who become pregnant after taking ellaOne should contact their doctor (see section 4.6). If the next menstrual period is more than 7 days late, if the menstrual period is abnormal in character or if there are symptoms suggestive of pregnancy or in case of doubt, a pregnancy test should be performed. As with any pregnancy, the possibility of an ectopic pregnancy should be considered. It is important to know that the occurrence of uterine bleeding does not rule out ectopic pregnancy. **Section 4.6 – Fertility, pregnancy and lactation** Pregnancy ellaOne is not intended for use during pregnancy and should not be taken by any woman suspected or known to be pregnant (see sections 4.2). ellaOne does not interrupt an existing pregnancy. 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. **Section 5.3- Preclinical safety data** Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity. Most findings in general toxicity studies were related to its mechanism of action as a modulator of progesterone and glucocorticoid receptors, with antiprogesterone activity observed at exposures similar to therapeutic levels. Information from reproductive toxicity studies is limited due to the absence of exposure measurement in these studies. Ulipristal acetate has an embryolethal effect in rats, rabbits (at repeated doses above 1 mg/kg) and in monkeys. At these repeated doses, the safety for a human embryo is unknown. At doses which were low enough to maintain gestation in the animal species, no teratogenic effects were observed. Carcinogenicity studies (in rats and mice) showed that ulipristal acetate is not carcinogenic. **Package leaflet** **1. What ellaone is and what it is used for** ellaOne is an emergency contraceptive ellaOne is a contraceptive intended to prevent pregnancy after unprotected sex or if your contraceptive method has failed.

Safety concern	**Effects on foetus and newborn**
	[…] ellaOne does not work if you are already pregnant. […] ellaOne is a contraceptive used to prevent a pregnancy from starting. If you are already pregnant, it will not interrupt an existing pregnancy. **Warning and precautions** Talk to your pharmacist, doctor or other healthcare professional before taking ellaOne: • if your period is late or you have symptoms of pregnancy (heavy breasts, morning sickness), as you may already be pregnant (see section "Pregnancy, breast-feeding and fertility") **Pregnancy, breast feeding and fertility** Before taking ellaOne, if your period is late, tell your pharmacist, doctor or other healthcare professional, or do a pregnancy test in order to make sure you are not already pregnant (see section "Warning and precautions"). ellaOne is a contraceptive used to prevent a pregnancy from starting. If you are already pregnant it will not interrupt an existing pregnancy . If you become pregnant despite taking ellaOne, there is no evidence that ellaOne will affect your pregnancy. However, it is important that you see your doctor. As for any pregnancy, your doctor may want to check that the pregnancy is not outside the womb. This is especially important if you have severe abdominal (stomach) pain or bleeding or if you have previously had a pregnancy outside the womb, tubal surgery or long term (chronic) genital infection. If you become pregnant despite taking ellaOne, you are encouraged to ask your doctor to register your pregnancy in an official registry. You can also report this information on your own at www.hra-pregnancy-registry.com.Your information will remain anonymous – nobody will know it is information about you. Sharing your information may help women in the future understand the safety or risks of ellaOne during a pregnancy.
	Comment (e.g. on any differences between SPCs) Not applicable.
	Other routine risk minimisation measures None
Additional risk minimisation measure(s) (repeat as necessary)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Effectiveness will be measured by means of routine pharmacovigilance activities.
Criteria for judging the success of the proposed risk minimisation measures	Comparison of product information versus ICSRs.
Planned dates for assessment	Assessment will be performed during medical review of ICSRs and in PSUR.
Results of effectiveness measurement	Results will be presented regularly in PSUR and RMP updates.
Impact of risk minimisation	Minimisation of the occurrence of the use by pregnant women.
Comment	None

Safety concern	**Risk of ectopic pregnancy**
Objective(s) of the risk minimisation measures	To inform about this potential risk as for any pregnancy and actions to be taken.
Routine risk minimisation measures	Text in SPC and package leaflet **SPC** **Section 4.4 – Special warnings and precautions for use** As with any pregnancy, the possibility of an ectopic pregnancy should be considered. It is important to know that the occurrence of uterine bleeding does not rule out ectopic pregnancy **Package leaflet** **Pregnancy, breast-feeding and fertility** If you become pregnant despite taking ellaOne, there is no evidence that ellaOne will affect your pregnancy. However, it is important that you see your doctor. As for any pregnancy, your doctor may want to check that the pregnancy is not outside the womb. This is especially important if you have severe abdominal (stomach) pain or bleeding or if you have previously had a pregnancy outside the womb, tubal surgery or long term (chronic) genital infection.
	Comment (e.g. on any differences between SPCs) Not applicable.
	Other routine risk minimisation measures None
Additional risk minimisation measure(s) (repeat as necessary)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Effectiveness will be measured by means of routine pharmacovigilance activities.
Criteria for judging the success of the proposed risk minimisation measures	Comparison of product information versus ICSRs.
Planned dates for assessment	Assessment will be performed during medical review of ICSRs and in PSUR.
Results of effectiveness measurement	Results will be presented regularly in PSUR and RMP updates.
Impact of risk minimisation	Not applicable
Comment	None

Safety concern	**Effect of concomitant use of CYP3A4 inducers**
Objective(s) of the risk minimisation measures	To inform about the potential risk and avoid concomitant use.
Routine risk minimisation measures	Text in SPC and package leaflet **SPC** **Section 4.4. –Special warnings and precautions for use** **Specific populations** Concomitant use of ellaOne with CYP3A4 inducers is not recommended due to interaction (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, efavirenz, fosphenytoine, nevirapine, oxcarbazepine, primidone, rifabutine, St John's wort/Hypericum perforatum, long term use of ritonavir). **Section 4.5. – Interaction with other medicinal products and other forms of interactions** Potential for other medicinal products to affect ulipristal acetate: Ulipristal acetate is metabolized by CYP3A4 in vitro. - *CYP3A4 inducers* In vivo results show that the administration of ulipristal acetate with a strong CYP3A4 inducer such as rifampicin markedly decreases Cmax and AUC of ulipristal acetate by 90% or more and decreases ulipristal acetate half-life by 2.2-fold corresponding to an approximately 10-fold decrease of ulipristal acetate exposure. Concomitant use of ellaOne with CYP3A4 inducers (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, efavirenz, fosphenytoine, nevirapine, oxcarbazepine, primidone, rifabutine, St John's wort/Hypericum perforatum) therefore reduces plasma concentrations of ulipristal acetate and may result in a decreased efficacy of ellaOne and is therefore not recommended. **Package leaflet** **Other medicines and ellaOne** Tell your pharmacist, doctor or other healthcare professional if you are taking, have recently taken or might take any other medicines. This is especially important if you are taking any of the medicines listed below since they make ellaOne work less well: Phenytoin, fosphenytoine, phenobarbital, primidone, carbamazepine, oxcarbazepine (used to treat epilepsy) Ritonavir, efavirenz, nevirapine (used to treat HIV infection) Rifampicin, rifabutin (used to treat tuberculosis) St John's wort (Hypericum perforatum) or herbal medicines that contain it (used for depression or anxiety)
	Comment (e.g. on any differences between SPCs) Not applicable.
	Other routine risk minimisation measures: None
Additional risk minimisation measure(s) (repeat as necessary)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Effectiveness will be measured by means of routine pharmacovigilance activities.
Criteria for judging the success of the proposed risk minimisation measures	Comparison of product information versus ICSRs.
Planned dates for assessment	Assessment will be performed during medical review of ICSRs and in PSUR.

Results of effectiveness measurement	Results will be presented regularly in PSUR and RMP updates.
Impact of risk minimisation	Not applicable
Comment	None

Safety concern	**Liver effects**
Objective(s) of the risk minimisation measures	None proposed. This potential risk has not been confirmed and no information is deemed necessary in the SPC.
Routine risk minimisation measures	Not applicable.
	Comment (e.g. on any differences between SPCs) Not applicable.
	Other routine risk minimisation measures Not applicable.
Additional risk minimisation measure(s)	Objective and justification of why needed Not applicable.
	Proposed actions/components and rationale Not applicable.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessment	Not applicable.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Not applicable.

Safety concern	**Delayed menstrual period > 60 days / amenorrhea**
Objective(s) of the risk minimisation measures	To inform about this potential risk through routine product labelling
Routine risk minimisation measures	**Text in SmPC** **Section 4.4. –Special warnings and precautions for use** After ellaOne intake menstrual periods can sometimes occur a few days earlier or later than expected. 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.
Additional risk minimisation measure(s) (repeat as necessary)	No additional risk minimisation measures are proposed in this RMP.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Effectiveness will be measured by means of routine pharmacovigilance activities.
Criteria for judging the success of the proposed risk minimisation measures	Comparison of product information versus ICSRs.
Planned dates for assessment	Assessment will be performed during medical review of ICSRs and in PSUR.
Results of effectiveness	Results will be presented regularly in PSUR and RMP updates.

Safety concern	**Delayed menstrual period > 60 days / amenorrhea**
measurement	
Impact of risk minimisation	Not applicable
Comment	None

Safety concern	**Ovarian cysts**
Objective(s) of the risk minimisation measures	To inform about this potential risk through routine product labelling
Routine risk minimisation measures	**Text in SmPC** **Section 4.8. – Undesirable effects** Reproductive system and breast disorders: Rare: Ruptured ovarian cyst
	Comment (e.g. on any differences between SmPCs) Not applicable.
	Not applicable
Additional risk minimisation measure(s) (repeat as necessary)	No additional risk minimisation measures are proposed in this RMP.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Effectiveness will be measured by means of routine pharmacovigilance activities.
Criteria for judging the success of the proposed risk minimisation measures	Comparison of product information versus ICSRs.
Planned dates for assessment	Assessment will be performed during medical review of ICSRs and in PSUR.
Results of effectiveness measurement	Results will be presented regularly in PSUR and RMP updates.
Impact of risk minimisation	Not applicable
Comment	None

Safety concern	**Effect of concomitant use of progestin-only contraception**
Objective(s) of the risk minimisation measures	To inform about the lack of information and warn against the potential interaction.
Routine risk minimisation measures	Text in SPC and package leaflet **SPC** **Section 4.4. –Special warnings and precautions for use** Although the use of ellaOne does not contraindicate the continued use of regular hormonal contraception, ellaOne may reduce its contraceptive action (see section 4.5). Therefore, if a woman wishes to start or continue using hormonal contraception, she can do so after using ellaOne, however, she should be advised to use a reliable barrier method until the next menstrual period. **Section 4.5. – Interactions** Potential for ulipristal acetate to affect other medicinal products: • Hormonal contraceptives Because ulipristal acetate binds the progesterone receptor with high affinity, it may interfere with the action of progestogen-containing medicinal products: - Contraceptive action of combined hormonal contraceptives and progestogen-only contraception may be reduced

Safety concern	**Effect of concomitant use of progestin-only contraception**
	- Concomitant use of ulipristal acetate and emergency contraception containing levonorgestrel is not recommended (see section 4.4). **Package leaflet** **What you need to know before you use ellaOne** Other contraceptives and ellaOne ellaOne may make regular hormonal contraceptives, like pills and patches, temporarily less effective. If you are currently taking hormonal contraception, continue to use it as usual after taking ellaOne, but be sure to use condoms every time you have sex until your next period. Do not use ellaOne together with another emergency contraceptive pill that contains levonorgestrel. By taking them both together, you might make ellaOne less effective.
	Comment (e.g. on any differences between SPCs) Not applicable.
	Other routine risk minimisation measures None
Additional risk minimisation measure(s) (repeat as necessary)	None
	-
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Effectiveness will be measured by means of routine pharmacovigilance activities.
Criteria for judging the success of the proposed risk minimisation measures	Comparison of product information versus ICSRs.
Planned dates for assessment	Assessment will be performed during medical review of ICSRs and in PSUR.
Results of effectiveness measurement	Results will be presented regularly in PSUR and RMP updates.
Impact of risk minimisation	Not applicable
Comment	None

Safety concern	**Effect in women with severe asthma treated by oral glucocorticoids**
Objective(s) of the risk minimisation measures	To acknowledge the limited information and warn against the potential interaction.
Routine risk minimisation measures	Text in SPC and in package leaflet **SPC** **Section 4.4. –Special warnings and precautions for use** **Specific populations** Use in women with severe asthma treated by oral glucocorticoid is not recommended. **Package leaflet** **Warning and precautions** Talk to your pharmacist, doctor or other healthcare professional before taking ellaOne • if you suffer from severe asthma
	Comment (e.g. on any differences between SPCs) Not applicable.
	Other routine risk minimisation measures None
Additional risk minimisation	None

Safety concern	**Effect in women with severe asthma treated by oral glucocorticoids**
measure(s) (repeat as necessary)	
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Effectiveness will be measured by means of routine pharmacovigilance activities.
Criteria for judging the success of the proposed risk minimisation measures	Comparison of product information versus ICSRs.
Planned dates for assessment	Assessment will be performed during medical review of ICSRs and in PSUR.
Results of effectiveness measurement	Results will be presented regularly in PSUR and RMP updates.
Impact of risk minimisation	Not applicable
Comment	None

Safety concern	**Effect in women with impaired liver function**
Objective(s) of the risk minimisation measures	To acknowledge the limited information.
Routine risk minimisation measures	Text in SPC and package leaflet **SPC** **Section 4.2. Posology and method of administration** Hepatic impairment In the absence of specific studies, no alternate dose recommendations for ellaOne can be made. Severe hepatic impairment In the absence of specific studies, ellaOne is not recommended. **Package leaflet** **Warning and precautions** Talk to your pharmacist, doctor or other healthcare professional before taking ellaOne • if you suffer from severe liver disease.
	Comment (e.g. on any differences between SPCs) Not applicable.
	Other routine risk minimisation measures None proposed
Additional risk minimisation measure(s) (repeat as necessary)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Effectiveness will be measured by means of routine pharmacovigilance activities.
Criteria for judging the success of the proposed risk minimisation measures	Comparison of product information versus ICSRs.
Planned dates for assessment	Assessment will be performed during medical review of ICSRs and in PSUR.
Results of effectiveness measurement	Results will be presented regularly in PSUR and RMP updates.
Impact of risk minimisation	Not applicable
Comment	None

V.2 Risk minimisation measure failure (if applicable)

Not applicable.

V.2.1 Analysis of risk minimisation measure(s) failure

Not applicable.

V.2.2 Revised proposal for risk minimisation

Not applicable.

V.3 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
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 and possibility of reduced action 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

PART VI SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY MEDICINAL PRODUCT

VI.1 Elements for summary tables in the EPAR

1.3.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Effect 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

1.3.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and 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 Category: 3	To assess clinical follow-up and outcome of pregnancies resulting from ellaOne failure or pregnancies inadvertently exposed to ellaOne.	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.

1.3.3 Summary of Post authorisation efficacy development plan

Not applicable.

1.3.4 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Effect on pregnancy maintenance / Off-label use	SPC and package leaflet Information in section 4.2 of the SPC Warning in section 4.4 Information in section 4.6	None
Risk of incomplete abortion and heavy bleeding	SPC and package leaflet Information in section 4.2 of the SPC Warning in section 4.4 of the SPC	None
Effects on foetus and newborn	SPC and package leaflet Information in section 4.2 of the SPC 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 of SPC Information in section 4.5.	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
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 and possibility of reduced action 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

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Despite the many highly effective contraceptive options women have to choose from, none is 100% perfect. Mistakes happen — a condom breaks, a woman misses a pill, or she has unplanned sex. Emergency contraception is a back-up birth control method that can prevent pregnancy after unprotected intercourse or contraceptive failure. It is estimated that approximately 5% of sexually active women in Europe use emergency contraception each year.

ellaOne is an emergency contraceptive to be taken within 120 hours (five days) of unprotected sex or contraceptive failure (such as a tear in a condom during sex).

VI.2.2 Summary of treatment benefits

Two oral methods of emergency contraception are available today: ellaOne and levonorgestrel.

Taking ellaOne significantly reduces a woman's chance of getting pregnant. In studies conducted in over 4000 women requesting emergency contraception, ellaOne reduced the chance of getting pregnant after unprotected sex from more than five percent to two percent.

In studies in which women were randomized to receive ellaOne or the other kind of emergency contraceptive pill, levonorgestrel, ellaOne was more effective.

VI.2.3 Unknowns relating to treatment benefits

Women who participated in the main studies of ellaOne were of a range of weights and ethnic origins and were primarily between 18 and 35 years old. Additional studies in adolescents produced consistent results.

VI.2.4 Summary of safety concerns

Important identified risks

ellaOne carries no important identified risks.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Harm to a pregnancy	ellaOne is intended to prevent pregnancy and is not to be used by pregnant women. A woman who takes ellaOne could fall pregnant several days later, in case of failure. A woman who does not realize she is pregnant could accidentally take ellaOne. Whatever the reason, if a woman takes ellaOne just before or soon after becoming pregnant, it is important to consider how her pregnancy could theoretically be affected: - she could miscarry and experience bleeding: this has been seen with extremely high doses in animals, but in studies of ellaOne, pregnant women were no more likely to miscarry nor did they have heavy bleeding - her baby could develop abnormally: no malformations have been observed in the offspring of female animals treated with ellaOne, and no harmful effects have been reported in babies due to their mother taking ellaOne, although the absolute number of babies born to date is low - her pregnancy could be ectopic (implant outside the womb): no ectopic pregnancies occurred in studies of ellaOne, but this possibility should be considered, as for all pregnancies. Since launch rare cases of ectopic pregnancy have been reported.

Risk	What is known (Including reason why it is considered a potential risk)
Use with certain medicines known as CYP3A4 inducers	Some medicines may make ellaOne less effective because of the way the body processes them in the liver.
Effects on the liver	Animals who received high repeated doses of ulipristal acetate had increased liver weights and enlargement of their liver cells. However, no significant abnormal liver function tests have been reported during any studies in women.
Long delay in menstrual period	ellaOne tends to delay a woman's next menstrual period by a few days, and in a small proportion of women the delay might be quite long. In studies, some 3% of women waited more than two months for their next period.
Ovarian cyst	Some ovarian cysts were reported in studies. Almost all disappeared within 1 month of taking ellaOne and only a few were found to rupture. The development of ovarian cysts is common with the use of hormonal contraceptives as well as some other drugs. These cysts usually disappear after a woman's next menses. No ovarian cysts have been reported as an adverse event since the launch of ellaOne.

Missing information

Risk	What is known
Limited information on use with progestin-only pills	Oral contraceptive users were not enrolled in studies of ellaOne. Because ellaOne binds to the same receptor as contraceptive minipills, their contraceptive action could theoretically be reduced. It is recommended that women use a back-up method of contraception (condom) until their next period.
Limited information on use in women with severe asthma treated by oral corticoids	ellaOne is not recommended for use in women with severe asthma, as none were enrolled in studies of ellaOne because ellaOne binds to the same receptor as the oral glucocorticoids used to treat asthma.
Limited information on use in women with liver impairment	ellaOne is metabolised in the liver, so liver impairment may impede its elimination from the body. No studies in patients with liver impairment have been performed.

VI.2.5 Summary of additional risk minimisation measures by safety concern

Not applicable

VI.2.6 Planned post authorisation development plan

Not applicable.

1.4 Summary of changes to the risk management plan over time

This chapter includes the latest change only as version 12 represents the first RMP in the new format as required by EU Good Pharmacovigilance Practice Module V.

Version	Date	Safety Concerns	Comment
Version 12	July 2013	**Identified risks:** no change	
		Potential risks removed: no change	
		Missing information removed:	
		• Effect in women with impaired renal function	The potential risk does not meet definition of missing information as per GVP.
Version 13	August 2014	**Identified risks removed:**	
		• None	
		Potential risks regrouped :	
		• Effects on foetus and newborns	This risk covers the previously listed risks named "Adverse pregnancy outcomes", "Unintended pregnancy exposure (risk of malformations)" and "Effects on pregnancy in case of treatment failure
		Potential risks reworded: • Effects on pregnancy maintenance /off label use • Risk of incomplete abortion and heavy bleeding	
		Missing information removed:	
		• Effects in post pubertal children	Based on interim results of PIP study
		• Efficacy and safety in repeated use in the same cycle	Based on the results of a repeat use study

PART VII ANNEXES TO THE RISK MANAGEMENT

A7. Annex 7 - Specific adverse event follow-up forms

Drug exposure during pregnancy (emergency contraception)	HRA Pharma
Page : 1 of 5	

Please return this form to HRA Pharma-Pharmacovigilance-15 rue Béranger-75003 PARIS, fax : 01.42.77.03.52, e-mail : pharmacovigilance@hra-pharma.com

HEALTH CARE PROVIDER INFORMATION		
Last name :	First name :	
Medical Specialty :		
Address :	Phone: Fax :	
E-mail :		
Date :	Signature :	
PATIENT IDENTIFICATION		
Initials :	Date of birth (DD/MM/YY) :	
Height:	Weight:	
PREGNANCY INFORMATION		
Date of last menstrual period :	Pregnancy stage at time of report :	
Date of diagnosis :	Expected delivery date :	
EMERGENCY CONTRACEPTION EXPOSURE		
Drug intake :	Date of drug intake :	
Total dose administered :	Batch number:	Exp. date:
Time from intercourse to drug intake (hours) :		
Pregnancy stage at drug exposure (in weeks) :		
Pregnancy status before emergency contraception intake : ☐ Not pregnant ☐ Pregnant		
Additional intake of HRA Pharma emergency contraception during pregnancy? ☐ no ☐ _yes: How many? ..... Period of exposure: ☐1ST TRIM. ☐2ND TRIM. ☐ 3RD TRIM. ☐ UNK		

PREGNANCY OUTCOME		
☐ Elective abortion (no medical reason)	Date of procedure :	Thank you for completing this form. No further information is requested.
☐ Live birth	☐ Healthy children Pregnancy term (weeks) _____ Number of children born _____ For each child, please specify : Sex : _____ Birth weight (kg) : _____ Sex : _____ Birth weight (kg) : _____ Sex : _____ Birth weight (kg) : _____	Thank you for completing this form. No further information is requested.
	☐ Congenital anomaly	Please complete pages 2 and 3
	☐ Neonatal death	Please complete pages 2 and 4
☐ Maternal death		Thank you for completing this form. You will be contacted very soon for further information.
☐ Induced therapeutic abortion (in case of anomaly discovered during a prenatal diagnosis)		Please complete pages 2 and 5
☐ Spontaneous abortion (<20 weeks of pregnancy)		Please complete pages 2 and 5
☐ Premature foetal death (20-27 weeks of pregnancy)		Please complete pages 2 and 5
☐ Premature foetal death (>28 weeks of pregnancy)		Please complete pages 2 and 5
☐ Ectopic pregnancy		Please complete pages 2 and 5

Linked to « COR_S&M_INS_EN_036 » COR_S&M_FOR_EN_018-03

Drug exposure during pregnancy (emergency contraception)

Page : 2 of 5

Patient ID: Initials Date of birth: / /

MATERNAL HISTORY

History of pregnancy	☐ no ☐ yes, how many ?__	If yes, number of live infants :_____	
History of spontaneous abortion (miscarriage)	☐ no ☐ yes, how many ?__	History of foetal death ?	☐ no ☐ yes, how many ?___
History of elective abortion ?	☐ no ☐ yes, how many ?__	History of therapeutic abortion ?	☐ no ☐ yes, how many ?___
History of birth defect ?	☐ no ☐ yes, how many ?__	History of congenital anomaly ?	☐ no ☐ yes, how many ?___

RELEVANT DRUG(S) OTHER THAN HRA PHARMA EMERGENCY CONTRACEPTION RECEIVED DURING PREGNANCY

Medication Name	Indication	Daily dose	Route of administration	Periode of exposure during pregnancy				
				1st trim.	2nd trim.	3rd trim.	Throughout pregnancy	Unknown
				☐	☐	☐	☐	☐
				☐	☐	☐	☐	☐
				☐	☐	☐	☐	☐

RECREATIONAL DRUG USE

Recreational drug use	Yes	No	Estimated weekly dose	Route of administration	Period of exposure during pregnancy				
					1st trim	2nd trim.	3rd trim.	Throughout pregnancy	Unknown
Tobacco	☐	☐			☐	☐	☐	☐	☐
Alcohol	☐	☐			☐	☐	☐	☐	☐
Illicit drugs	☐	☐			☐	☐	☐	☐	☐

RELEVANT MEDICAL CONDITION(S) DURING PREGNANCY*

*diabetes, hypertension or any other significant medical condition

Medical condition	Start date	Stop date	Ongoing at the time of pregnancy outcome
			☐
			☐
			☐

RESULTS OF SEROLOGY TESTS

Rubella test	Date and Result
Toxoplasmosis test	Date and Result

PRENATAL TESTS

Type of test	Date and Result

In case of congenital anomaly, please complete page 3
In case of neonatal death, please complete page 4
In case of foetal loss, please complete page 5

COR_S&M_FOR_EN_018-03

Drug exposure during pregnancy (emergency contraception)

Page : 3 of 5

Patient ID: Initials Date of birth: / /

TO COMPLETE IN CASE OF CONGENITAL ANOMALY		
Pregnancy term (in weeks): _____ Number of children born : _____	Delivery method : □ Vaginal □ Caesarean	
CHILD	LIST OF CONGENITAL ANOMALIES	
1		
2		
3		
CHILD	RELATIONSHIP TO EMERGENCY CONTRACEPTION INTAKE (certain/probable/possible/unlikely/not related)	POSSIBLE CAUSES 1=MATERNAL AGE, 2=UNKNOWN 3=OTHER, SPECIFY
1		
2		
3		

APGAR SCORES		
CHILD	APGAR 1 MIN	APGAR 5 MIN
1		
2		
3		

Please describe below any maternal and/or family history of congenital anomaly

Please describe below any other significant maternal and/or family history

Other comments

Thank you for completing this form.

COR_S&M_FOR_EN_018-03

Drug exposure during pregnancy (emergency contraception)

Page : 4 of 5

Patient ID: Initials Date of birth: / /

TO COMPLETE IN CASE OF NEONATAL DEATH

Pregnancy term (in weeks): _____
Number of children born : _____

Delivery method :
□ Vaginal □ Caesarean

CHILD	AGE OF NEONATE AT DEATH	CAUSE OF DEATH	RELATIONSHIP TO EMERGENCY CONTRACEPTION INTAKE (certain/probable/possible/unlikely/not related)	AUTOPSY PERFORMED (YES/NO)
1				
2				
3				

APGAR SCORES

CHILD	APGAR 1 MIN	APGAR 5 MIN
1		
2		
3		

Please describe below any maternal and/or family history of neonatal death

Please describe below any other significant maternal and/or family history

Other comments

Thank you for completing this form.

COR_S&M_FOR_EN_018-03

Drug exposure during pregnancy (emergency contraception)

Page : 5 of 5

Patient ID: Initials _____ Date of birth: ____/____/_____

TO COMPLETE IN CASE OF FOETAL LOSS	
Pregnancy term (in weeks) at time of foetal loss: _____ Number of foetus : _____	
FACTORS THAT MAY HAVE HAD AN IMPACT ON FŒTAL LOSS	
1	
2	
3	
4	
5	
In case of ectopic pregnancy, please specify below : □ Salpingitis or known tubal anomaly □ Previous ectopic pregnancy □ Previous tubal surgery	
RELATIONSHIP BETWEEN FŒTAL LOSS AND EMERGENCY CONTRACEPTION INTAKE (certain / probable / possible / unlikely / not related) : _____	
Please describe below any maternal and/or family history of foetal loss	
Please describe below any other significant maternal and/or family history	
FŒTAL LOSS COMPLICATIONS	
Any vaginal bleeding?	☐ no ☐ yes, please specify : □ Spotting □ Regular □ Heavy Duration of bleedings: _____ Were the bleedings clinically excessive? □ no □ yes
Need for a curettage?	☐ no ☐ yes: Please specify the gestational age: _____ The curettage was performed: □ following the usual protocol □ because you were worried about excessive bleeding
Any infection?	☐ no ☐ yes, please specify: □ Location of infection _____ □ Infectious agent_____ □ Treatment given _____ Was the infection a complication of pregnancy loss? □ no □ yes
Any other complication?	☐ no ☐ yes, please describe:
OTHER COMMENTS	

Thank you for completing this form.

COR_S&M_FOR_EN_018-03

ADVERSE REACTION LIVER INJURY

HRA Pharma

Page: **1 of 2**

1. Country	2. DRUG	5. REPORTER Name: Address: Tel.:
3. Date of this report:	4. Identification N°	

I. THE PATIENT

6. INITIALS (first, last): 7. SEX: 8. AGE 9. WEIGHT:
10. OCCUPATION: 11. COUNTRY OF ORIGIN 12. OTHER:

13. PREVIOUS RELEVANT HISTORY AND CONCURRENT DISORDERS:

	no	yes	Specify
Current pregnancy	☐	☐	
Hepato-biliary	☐	☐	
Allergic disease	☐	☐	
Allergy to drug	☐	☐	
Auto-Immune	☐	☐	
Heart/vascular diseases	☐	☐	
Respiratory	☐	☐	

	no	yes	Specify
Cancer	☐	☐	
Surgical operation (dental) Date:	☐	☐	
Transfusion of blood or derivatives Date:	☐	☐	
Alcohol, consumption			
Acupuncture	☐	☐	Date:

	no	yes
Occupational toxic agent Specify:	☐	☐
Travels: Africa, Asia	☐	☐
Intravenous drug abuse	☐	☐
Other:		

II. THE ADVERSE REACTION

14. DATE OF ONSET

15. NATURE OF FIRST SYMPTOMS

	no	yes	Date
Abdominal pain	☐	☐	
Vomiting	☐	☐	
Skin eruption Type:	☐	☐	
Purpura	☐	☐	

16. DESCRIPTION

	no	yes	Date
Asthenia	☐	☐	
Fever	☐	☐	
Pruritis	☐	☐	
Jaundice	☐	☐	
Joint pain	☐	☐	

	no	yes	Date
Hepatomegaly	☐	☐	
Splenomegaly	☐	☐	
Lymph nodes	☐	☐	
Ascites	☐	☐	
Asterixis	☐	☐	
Coma	☐	☐	

17. LABORATORY DATA - Before/During/After treatment *(if necessary, continued overleaf)*

DATES				
SGOT/SGPT (N</)				
Alkaline Ph. (N<)				
GGT (N<)				
CPK (N<)				
Bilirubin				
Conjugated bilirubin				
γglobulins (g/l)				
P.T. (%)				
Factor V (%)				
Hemoglobin (g/dl)				
Leukocytes				
Neutrophils				
Eosinos				
Creatininemia (units)				
Urea				

Dates	Not tested	Absent	Present	Titre
HBs Ag	☐	☐	☐	
Anti-Hbs Ab	☐	☐	☐	
Anti-Hbc Ab	☐	☐	☐	
Anti-Hbc/IgM Ab	☐	☐	☐	
Anti-HAV/IgM Ab	☐	☐	☐	
Anti-HCV Ab	☐	☐	☐	
Anti-CMV IgM Ab	☐	☐	☐	
Anti-EBV Ab	☐	☐	☐	
Anti nuclear Ab	☐	☐	☐	
Antinative DNA Ab	☐	☐	☐	
Anti smooth muscle Ab	☐	☐	☐	
Antimitochondria Ab	☐	☐	☐	

18. ULTRASONOGRAPHY

☐ no ☐ yes Date:

☐ normal

☐ abnormal *(brief results)*

19. LIVER BIOPSY

☐ no ☐ yes Date:

Results
(attach report)

20. OUTCOME *(tick more than one box if necessary)*

☐ no hospitalization ☐ complete recovery
☐ Hospitalization / Prolonged hospitalization
☐ Recovery with sequelea
Specify

☐ Death date:
Cause

Relationship between the reaction and the death
☐ Not assessable ☐ Unlikely ☐ Likely

III. SUSPECTED DRUG

21. Name

22. Indication

23. Daily dose

24. Route

25. Date beginning

26. Date end

27. Duration

28. ADMINISTRATION OF THE DRUG AFTER THE BEGINNING OF THE REACTION
☐ Stopped
☐ Continued (same dose)
☐ Reduced (dose):
☐ Other:

29. IMMEDIATE RESULT
☐ Improvement ☐ No change
☐ Aggravation ☐ Uninterpretable

30. READMINISTRATION OF THE DRUG
☐ no
☐ yes dose: date:
And, if yes:

31. RECURRENCE OF THE REACTION
☐ no ☐ yes, date
☐ Uninterpretable

32. PREVIOUS THERAPY WITH THE SAME DRUG
☐ no ☐ yes, date
Safety issues:

Formulary: DPV_FO_EN_012 version 2

ADVERSE REACTION LIVER INJURY

Page: 2 of 2

PATIENT INITIALS (first,last) :				SEX :		
IV. CONCOMITANT THERAPY *(continue overleaf if necessary)*						
33. DRUGS	Route	Daily dose	Duration	Dates of administration		Indications
				Beginning	End	
34. CAUSAL RELATIONSHIP : *(Reporter's assessment)*	☐ Not assessable	☐ Unrelated	☐ Unlikely	☐ Possible	☐ Probable	☐ Highly probable
35. Has this case been reported to a Regulatory Agency?	☐ No	☐ Yes	To whom?	Date:		

Formulary: DPV_FO_EN_012 version 2

A10. Annex 10 - Details of proposed additional risk minimisation measures

Not applicable