1. NAME OF THE MEDICINAL PRODUCT

Ella 30 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg ulipristal acetate.

Excipients with known effect:
Each tablet contains 237 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White to marble creamy, round curved tablet engraved with code *"ella"* on both faces.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
The treatment consists of one tablet to be taken orally as soon as possible, but no later than 120 hours (5 days) after unprotected intercourse or contraceptive failure.

The tablet can be taken with or without food.

If vomiting occurs within 3 hours of Ella intake, another tablet should be taken.

Ella can be taken at any moment during the menstrual cycle.

Pregnancy should be excluded before Ella is administered.

Special populations

Renal or hepatic impairment:
In the absence of specific studies, no specific dose recommendations for Ella can be made.

Severe hepatic impairment:
In the absence of specific studies, Ella is not recommended.

Children and adolescents:
A limited number of women under 18 years were included in clinical trials of Ella.

Method of administration
Oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy.

4.4 Special warnings and precautions for use

Concomitant use of ulipristal acetate with an emergency contraceptive containing levonorgestrel is not recommended (see section 4.5).

Use in women with severe asthma insufficiently controlled by oral glucocorticoid is not recommended**.**

Emergency contraception with Ella is an occasional method. It should in no instance replace a regular contraceptive method. In any case, women should be advised to adopt a regular method of contraception.

Although the use of Ella does not contraindicate the continued use of regular hormonal contraception, Ella may reduce its contraceptive action (see section 4.5). Therefore, after using emergency contraception, it is recommended that subsequent acts of intercourse be protected by a reliable barrier method until the next menstrual period starts. If a woman wishes to initiate hormonal contraception as a regular contraception method, she can do so immediately after using Ella, but the woman should use a reliable barrier method until the next menstrual period.

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

Emergency contraception with Ella does not prevent pregnancy in every case. No data is available on the efficacy of Ella for women who have had unprotected intercourse more than 120 hours before Ella intake. Limited and inconclusive data suggest that there may be reduced efficacy of Ella 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. In case of doubt, delay of more than 7 days in next menstrual period, abnormal bleeding at the expected date of menses, or symptoms of pregnancy, pregnancy should be excluded by a pregnancy test.

If pregnancy occurs after treatment with Ella, as for all pregnancies, the possibility of an ectopic pregnancy should be considered. Ectopic pregnancy may continue, despite the occurrence of uterine bleeding.

After Ella intake menstrual periods can sometimes occur earlier or later than expected by a few days. In approximately 7% of the women, menstrual periods occurred more than 7 days earlier than expected. In 18.5% of the women a delay of more than 7 days occurred, and in 4% the delay was greater than 20 days.

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Concomitant use of Ella with CYP3A4 inducers is not recommended due to potential for interaction (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, efavirenz, fosphenytoine, nevirapine, oxcarbazepine, primidone, rifabutine, St John's wort/Hypericum perforatum).

The CYP3A4 inhibitor ritonavir can also have an inducing effect on CYP3A4 when ritonavir is used for a longer period. In such cases ritonavir might reduce plasma concentrations of ulipristal acetate. Concomitant use is therefore not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect ulipristal acetate

Ulipristal acetate is metabolized by CYP3A4 *in vitro*.

- *CYP3A4 inhibitors*

  In vivo results show that administration of ulipristal acetate with a potent and a moderate CYP3A4 inhibitor increased C_{max} and AUC of ulipristal acetate with a maximum of 2- and 5.9-fold, respectively. The effects of CYP3A4 inhibitors are unlikely to have any clinical consequences.

  The CYP3A4 inhibitor ritonavir can also have an inducing effect on CYP3A4 when ritonavir is used for a longer period. In such cases ritonavir might reduce plasma concentrations of ulipristal acetate. Concomitant use is therefore not recommended (see section 4.4). Enzyme induction wears off slowly and effects on the plasma concentrations of ulipristal acetate may occur even if a woman has stopped taking an enzyme inducer within the last 2-3 weeks.

- *CYP3A4 inducers*

  In vivo results 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. Concomitant use of Ella 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 Ella and is therefore not recommended (see section 4.4).

Medicinal products affecting gastric pH

Administration of ulipristal acetate (10 mg tablet) together with the proton pump inhibitor esomeprazole (20 mg daily for 6 days) resulted in approximately 65% lower mean C_{max}, a delayed T_{max} (from a median of 0.75 hours to 1.0 hours) and 13% higher mean AUC. The clinical relevance of this interaction for single dose administration of ulipristal acetate as emergency contraception is not known.

Potential for ulipristal acetate to affect other medicinal products

In vitro data indicate that ulipristal acetate and its active metabolite do not significantly inhibit CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4, at clinically relevant concentrations. After single dose administration induction of CYP1A2 and CYP3A4 by ulipristal acetate or its active metabolite is not likely. Thus, administration of ulipristal acetate is unlikely to alter the clearance of medicinal products that are metabolised by these enzymes.

P-gp (P-glycoprotein) substrates

In vitro data indicate that ulipristal acetate may be an inihibitor of P-gp at clinically relevant concentrations. Results in vivo with P-gp substrate fexofenadine were inconclusive. The effects of ulipristal acetate on the P-gp substrates are unlikely to have any clinical consequences.

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
- Concomitant use of ulipristal acetate and emergency contraception containing levonorgestrel is not recommended (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Ella is contra-indicated during an existing or suspected pregnancy (see section 4.3).

Extremely limited data are available on the health of the foetus/new-born in case a pregnancy is exposed to ulipristal acetate. Although no teratogenic potential was observed, animal data are insufficient with regard to reproduction toxicity (see section 5.3).

HRA Pharma maintains a pregnancy registry to monitor outcomes of pregnancy in women exposed to Ella. Patients and health care providers are encouraged to report any exposure to Ella by contacting the Marketing Authorisation Holder.

Breast-feeding
Ulipristal acetate is excreted in breast milk (see section 5.2). The effect on newborn/infants has not been studied. A risk to the breastfed child cannot be excluded. After intake of Ella 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.

Fertility
A rapid return of fertility is likely following treatment with Ella for emergency contraception; therefore regular contraception should be continued or initiated as soon as possible following use of Ella to ensure ongoing prevention of pregnancy. Advice on how to proceed is presented in section section 4.4.

4.7 Effects on ability to drive and use machines

Ella may have minor or moderate influence on the ability to drive or use machines: mild to moderate dizziness is common after Ella intake, somnolence and blurred vision are uncommon; disturbance in attention has been rarely reported. The patient should be informed not to drive or use machines if they are experiencing such symptoms (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions were headache, nausea, abdominal pain and dysmenorrhea.

Safety of ulipristal acetate has been evaluated in 4,718 women during the clinical development program.

Table list of adverse reactions
The adverse reactions reported in the phase III program of 2,637 women are provided in the table below.
Adverse reactions listed below are classified according to frequency and system organ class. Within each frequency grouping, adverse reactions are presented in order of decreasing frequency.
The table lists adverse reactions according to system organ class and frequency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000)

MedDRA	Adverse reactions (frequency)		
System Organ Class	**Common**	**Uncommon**	**Rare**
Infections and infestations		Influenza	
Immune system disorders			hypersensitivity reactions including rash, urticaria, angioedema**
Metabolism and nutrition disorders		Appetite disorders	
Psychiatric disorders	Mood disorders	Emotional disorder Anxiety Insomnia Hyperactivity disorder Libido changes	Disorientation
Nervous system disorders	Headache Dizziness	Somnolence Migraine	Tremor Disturbance in attention Dysgueusia Syncope
Eye disorders		Visual disturbance	Abnormal sensation in eye Ocular hyperaemia Photophobia
Ear and labyrinth disorders			Vertigo
Respiratory, thoracic and mediastinal disorders			Dry throat
Gastrointestinal disorders	Nausea* Abdominal pain* Abdominal discomfort Vomiting*	Diarrhoea Dry mouth Dyspepsia Flatulence	
Skin and subcutaneous tissue disorders		Acne Skin lesion Pruritus	
Musculoskeletal and connective tissue disorders	Myalgia Back pain		
Reproductive system and breast disorders	Dysmenorrhea Pelvic pain Breast tenderness	Menorrhagia Vaginal discharge Menstrual disorder Metrorrhagia Vaginitis Hot flush Premenstrual syndrome	Genital pruritus Dyspareunia Ruptured ovarian cyst Vulvovaginal pain Hypomenorrhea*
General disorders and administration site conditions	Fatigue	Chills Malaise Pyrexia	Thirst

*Symptom which could be related to a pregnancy (and thus to a possible ectopic pregnancy) and could delay the diagnosis of pregnancy if misdiagnosed as related to drug intake
**Adverse reaction from spontaneous reporting

Post-marketing experience: the adverse reactions spontaneously reported in post-marketing experience were similar in nature to the safety profile described during the phase III program.

Description of selected adverse reactions
The majority of women (74.6%) in the phase III studies had their next menstrual period at the expected time or within ± 7 days, while 6.8% experienced menses more than 7 days earlier than expected and

18.5% had a delay of more than 7 days beyond the anticipated onset of menses. The delay was greater than 20 days in 4 % of the women.

A minority (8.7%) of women reported intermenstrual bleeding lasting an average of 2.4 days. In a majority of cases (88.2%), this bleeding was reported as spotting. Among the women who received Ella in the phase III studies, only 0.4% reported heavy intermenstrual bleeding.

In the phase III studies, 82 women entered a study more than once and therefore received more than one dose of Ella (73 women enrolled twice and 9 enrolled three times). There were no safety differences in these subjects in terms of incidence and severity of adverse events, change in duration or volume of menses or incidence of intermenstrual bleeding.

4.9 Overdose

Experience with ulipristal acetate overdose is limited. Single doses up to 200 mg have been used in women without safety concern. Such high doses were well-tolerated; however, these women had a shortened menstrual cycle (uterine bleeding occurring 2-3 days earlier than would be expected) and in some women, the duration of bleeding was prolonged, although not excessive in amount (spotting). There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, emergency contraceptives ATC code: G03AD02.

Ulipristal acetate is an orally-active synthetic selective progesterone receptor modulator which 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 also has high affinity for the glucocorticoid receptor and *in vivo*, in animals, antiglucocorticoid effects have been observed. However, in humans, no such effect has been observed even after repeat administration at the daily dose of 10 mg. It has minimal affinity to the androgen receptor and no affinity for the human estrogen or mineralocorticoid receptors.

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

Randomized controlled trial	Pregnancy rate (%) within 72h of unprotected intercourse or contraceptive failure[1]		Odds ratio [95% CI] of pregnancy risk, ulipristal acetate vs levonorgestrel[1]
	Ulipristal acetate	Levonorgestrel	
HRA2914-507	0.91 (7/773)	1.68 (13/773)	0.50 [0.18-1.24]
HRA2914-513	1.78 (15/844)	2.59 (22/852)	0.68 [0.35-1.31]
Meta-analysis	1.36 (22/1617)	2.15 (35/1625)	0.58 [0.33-0.99]

1 – Glasier et al, Lancet 2010

Two trials provide efficacy data on Ella used up to 120 hours after unprotected intercourse. In an open-label clinical trial, which enrolled women who presented for emergency contraception and were

treated with ulipristal acetate between 48 and 120 hours after unprotected intercourse, a pregnancy rate of 2.1% (26/1241) was observed. In addition, the second comparative trial described above also provides data on 100 women treated with ulipristal acetate from 72 to 120 hours after unprotected intercourse, in whom no pregnancies were observed.

Limited and inconclusive data from clinical trials suggest a possible trend for a reduced contraceptive efficacy of ulipristal acetate with high body weight or BMI (see section 4.4). The meta-analysis presented below excluded women who had further acts of unprotected intercourse.

Table 1: Meta-analysis on four clinical studies conducted with ulipristal acetate

BMI (kg/m^2)	**Underweight 0-18.5**	**Normal 18.5- 25**	**Overweight 25-30**	**Obese 30-**
N total	128	1866	699	467
N pregnancies	0	23	9	12
Pregnancy rate	0.00%	1.23%	1.29%	2.57%
Confidence Interval	0.00-2.84	0.78-1.84	0.59-2.43	1.34-4.45

5.2 Pharmacokinetic properties

Absorption
Following oral administration of a single 30 mg dose, ulipristal acetate is rapidly absorbed, with a peak plasma concentration of 176 ± 89 ng/ml occurring approximately 1 hour (0.5-2.0 h) after ingestion, and with an $AUC_{0-\infty}$ of 556 ± 260 ng.h/ml.

Administration of ulipristal acetate together with a high-fat breakfast resulted in approximately 45% lower mean Cmax, a delayed Tmax (from a median of 0.75 hours to 3 hours) and 25% higher mean $AUC_{0-\infty}$ compared with administration in the fasted state. Similar results were obtained for the active mono-demethylated metabolite.

Distribution
Ulipristal acetate is highly bound (>98%) to plasma proteins, including albumin, alpha-l-acid glycoprotein, and high density lipoprotein.

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

In vitro data indicate that ulipristal acetate may be an inhibitor of BCRP (Breast Cancer Resistance Protein) transporters at the intestinal level. The effects of ulipristal acetate on BCRP are unlikely to have any clinical consequences.

Ulipristal acetate is not a substrate for either OATP1B1 or OATP1B3.

Biotransformation/elimination
Ulipristal acetate is extensively metabolized to mono-demethylated, di-demethylated and hydroxylated metabolites. The mono-demethylated metabolite is pharmacologically active. In vitro data indicate that this is predominantly mediated by CYP3A4, and to a small extent by CYP1A2 and CYP2A6. The terminal half-life of ulipristal acetate in plasma following a single 30 mg dose is estimated to 32.4 ± 6.3 hours, with a mean oral clearance (CL/F) of 76.8 ± 64.0 L/h.

Special populations
No pharmacokinetic studies with ulipristal acetate have been performed in females with impaired renal or hepatic function.

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.

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

Carcinogenicity studies (in rats and mice) showed that ulipristal acetate is not carcinogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Povidone K30
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Protect from light. Store at or below 30ºC.

6.5 Nature and contents of container

PVC-PE-PVDC-Aluminium blister of 1 tablet.

The carton contains one blister of one tablet.

6.6 Special precautions for disposal

No special requirements

7. MANUFACTURER

CENEXI
17, rue de Pontoise
95520 Osny,
France

8. DATE OF REVISION OF THE TEXT

15 March 2022