PROFESSIONAL INFORMATION FOR ELLA

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

Ella.

30 mg tablet (uncoated).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg ulipristal acetate.

Excipients with known effect:

Each tablet contains 237 mg of 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 “ella” on both sides.

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 at any time during the menstrual cycle.

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

If the patient's menstrual period is late or in case of symptoms of pregnancy, **pregnancy should be excluded before the tablet is administered.**

Special populations

Renal impairment

No dose adjustment is necessary.

Hepatic impairment

In the absence of specific studies, no alternate dose recommendations for ELLA can be made.

Severe hepatic impairment

In the absence of specific studies, ELLA is not recommended.

Paediatric population

There is no relevant use of ELLA for children of prepubertal age in the indication emergency contraception.

Adolescents:

ELLA for emergency contraception is suitable for any woman of child bearing age, including adolescents. No differences in safety or efficacy have been shown compared to adult women aged 18 and older (see section 5.1).

Method of administration

Oral use.

The tablet can be taken with or without food.

4.3 Contraindications

Hypersensitivity to ulipristal acetate or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Before ELLA is taken pregnancy should be excluded.

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

ELLA is not intended for use during pregnancy and should not be taken by any woman suspected or known to be pregnant. However, it does not interrupt an existing pregnancy (see section 4.6).

ELLA does not prevent pregnancy in every case

In case 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. 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. Women who become pregnant after taking ELLA should contact their doctor (see section 4.6).

ELLA inhibits or postpones ovulation (see section 5.1). If ovulation has already occurred, it is no longer effective. The timing of ovulation cannot be predicted and therefore the tablet should be taken as soon as possible after unprotected intercourse.

No data are available on the efficacy of ELLA when taken more than 120 hours (5 days) after unprotected intercourse.

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.

After the tablet 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.

Concomitant use of ELLA and emergency contraception containing levonorgestrel is not recommended (see section 4.5).

Contraception after ELLA intake

ELLA is an emergency contraceptive that decreases pregnancy risk after unprotected intercourse but does not confer contraceptive protection for subsequent acts of intercourse. Therefore, after using emergency contraception, women should be advised to use a reliable barrier method until her next menstrual period.

Although the use of ELLA for emergency contraception does not contraindicate the continued use of regular hormonal contraception, ELLA 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 ELLA, however, she should be advised to use a reliable barrier method until the next menstrual period.

Specific populations

Concomitant use of ELLA with CYP3A4 inducers is not recommended due to interaction (e.g. barbiturates (including primidone and phenobarbital), phenytoin, fosphenytoin, carbamazepine, oxcarbazepine, herbal medicines containing *Hypericum perforatum* (St. John's wort), rifampicin, rifabutin, griseofulvin, efavirenz, nevirapine and long-term use of ritonavir).
Use in women with severe asthma treated by oral glucocorticoid is not recommended.
This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Potential for other medicines to affect ELLA

Ulipristal acetate is metabolised 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 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 ELLA with CYP3A4 inducers (e.g. barbiturates (including primidone and phenobarbital), phenytoin, fosphenytoin, carbamazepine, oxcarbazepine, herbal medicines containing *Hypericum perforatum* (St. John's wort), rifampicin, rifabutin, griseofulvin, efavirenz and nevirapine) therefore reduces plasma concentrations of ulipristal acetate and may result in a decreased efficacy of ELLA. For women who have used enzyme-inducing drugs in the past 4 weeks, ELLA is not recommended (see section 4.4) and non-hormonal emergency contraception (i.e. a copper intrauterine device (Cu-IUD)) should be considered.

- *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 in the past 4 weeks.

Medicines 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 ELLA as emergency contraception is not known.

Potential for ELLA to affect other medicines

Hormonal contraceptives

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

- Contraceptive action of combined hormonal contraceptives and progestogen-only contraception may be reduced
- Concomitant use of ELLA and emergency contraception containing levonorgestrel is not recommended (see section 4.4).

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 ELLA is unlikely to alter the clearance of medicines that are metabolised by these enzymes.

P-glycoprotein (P-gp) substrates

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

4.6 Fertility, pregnancy and lactation

Pregnancy

ELLA is not intended for use during pregnancy and should not be taken by any woman suspected or known to be pregnant (see section 4.2).

ELLA does not interrupt an existing pregnancy.

Pregnancy may occasionally occur after ELLA intake. Limited human data regarding pregnancy exposure to ELLA do not suggest any safety concern. Nevertheless, it is important that any pregnancy in a woman who has taken ELLA be reported to Cipla Medpro (Pty) Ltd at drugsafetysa@cipla.com or telephone 080 222 6662 (toll free) or to SAHPRA via the "Med Safety APP" (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Breastfeeding

ELLA 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 for emergency contraception, 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. Women should be advised to use a reliable barrier method for all subsequent acts of intercourse until the next menstrual period.

4.7 Effects on ability to drive and use machines

ELLA has 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

Safety of ELLA has been evaluated in 4 718 women during the clinical development program. The most commonly reported adverse reactions were headache, nausea, abdominal pain and dysmenorrhoea.

Tabulated list of adverse reactions

The adverse reactions reported in the phase III program of 2,637 women are provided in the table below.

Body System	**Frequency of adverse reactions**		
	Common (≥ 1/100 to 1/10)	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**
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 Dysgeusia 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	Dysmenorrhoea Pelvic pain Breast tenderness	Menorrhagia Vaginal discharge Menstrual disorder Metrorrhagia Vaginitis Hot flush Premenstrual syndrome	Genital pruritus Dyspareunia Ruptured ovarian cyst Vulvovaginal pain Hypomenorrhoea*
General disorders and administration site conditions	Fatigue	Chills Malaise Pyrexia	Thirst

*Symptom which could also be related to an undiagnosed pregnancy (or related complications).

**Adverse reaction from spontaneous reporting

Adolescents: the safety profile observed in women less than 18 years old in studies and post-marketing is similar to the safety profile in adults during the phase III program (see section 4.2).

Post-marketing experience: the adverse reactions spontaneously reported in post-marketing experience were similar in nature and frequency 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 reactions, change in duration or volume of menses or incidence of intermenstrual bleeding.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions. Suspected adverse reactions can be reported to Cipla Medpro (Pty) Ltd at drugsafetysa@cipla.com or telephone 080 222 6662 (toll free).

Suspected adverse reactions can also be reported to SAHPRA via the “Med Safety APP” (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Experience with ulipristal acetate overdose is limited. Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

A 18.8 Ovulation controlling agents

Ulipristal acetate is a selective progesterone receptor modulator which acts via high-affinity binding to the human progesterone receptor. When used for emergency contraception the mechanism of action is inhibition or delay of ovulation via suppression of the luteinising hormone (LH) surge. Pharmacodynamic data show that even when taken immediately before ovulation is scheduled to occur (when LH has already started to rise), ulipristal acetate is able to postpone follicular rupture for at least 5 days in 78,6 % of cases (p<0,005 vs. levonorgestrel and vs. placebo) (see table).

Prevention of ovulation[1,§]			
	Placebo n=50	**Levonorgestrel** n=48	**Ulipristal acetate** n=34
Treatment before LH surge	n=16 0,0 %	n=12 25,0 %	n=8 100 % p<0,005*
Treatment after LH surge but before LH peak	n=10 10,0 %	n=14 14,3 % NS†	n=14 78,6 % p<0,005*
Treatment after LH peak	n=24 4,2 %	n=22 9,1 % NS†	n=12 8,3 % NS*

1: Brache et al, Contraception 2013

§: defined as presence of unruptured dominant follicle five days after late follicular-phase treatment

*: compared to levonorgestrel

NS: non statistically significant

†: compared to placebo

Ulipristal acetate also has high affinity for the glucocorticoid receptor and *in vivo*, in animals, anti-glucocorticoid 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 oestrogen or mineralocorticoid receptors.

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 of the four clinical studies conducted with ulipristral acetate presented below excluded women who had further acts of unprotected intercourse.

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

A post-marketing observational study evaluating efficacy and safety of ELLA in adolescents aged 17 and younger showed no difference in the safety and efficacy profile compared to adult women aged 18 and older.

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 hours) 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 C_{max}, a delayed T_{max} (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-1-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 metabolised 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Povidone

Croscarmellose sodium

Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

PVC-PE-PVDC / Aluminium blister of 1 tablet or PVC-PVDC / Aluminium blister of 1 tablet. Each carton contains one blister.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

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Junxion Park

10 Elephant Lane

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Customer Care: 080 222 6662 .

8. REGISTRATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 November 2020

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