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TRANSPARENCY COMMITTEE

OPINION

13 January 2010

ELLAONE 30 mg, tablet
B/1(CIP: 394 503-7)

Applicant: HRA PHARMA

Ulipristal acetate

ATC code (2009): not yet attributed.
Pharmacotherapeutic category: G03X

List I

Date of Marketing Authorisation and corrections: 15 May 2009 (centralised procedure)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Ulipristal acetate

1.2. Background
First selective progesterone receptor modulator to have received marketing authorisation as emergency contraception within five days after unprotected sexual intercourse.

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

1.4. Dosage
“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 Ellaone intake, another tablet should be taken.
Ellaone can be taken at any moment during the menstrual cycle.
Pregnancy should be excluded before Ellaone is administered.
Renal or hepatic impairment: in the absence of specific studies, no specific dose recommendation can be made.
Severe hepatic impairment: in the absence of specific studies, Ellaone is not recommended.
Children and adolescents: safety and efficacy of Ellaone was only established in women 18 years and older.”

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)
ATC code not yet attributed.
May come under:
G : Genito-urinary system and sex hormones
G03 : Sex hormones and modulators of the genital system
G03X : Other sex hormones and modulators of the genital system

2.2. Medicines in the same therapeutic category
There is no other selective progesterone receptor modulator which has received marketing authorisation for use as emergency contraception.

2.3. Medicines with a similar therapeutic aim
Other levonorgestrel-based medicines indicated for use as emergency contraception:
Norlevo 1.5 mg tablet and Lévonorgestrel Biogaran 1.5 mg tablet, indicated for use as “Emergency contraception within 72 hours after unprotected sexual intercourse or contraceptive failure.”

2.4. Other contraceptives
Copper-based intrauterine devices (GYNELLE, MONA LISA) are indicated for “Emergency contraception if at-risk intercourse took place less than 120 hours ago. Associated pelvic infections must be taken into account.”

3. ANALYSIS OF AVAILABLE DATA

The pharmaceutical company submitted three clinical studies (including one phase II study in which a non-micronised form at 50 mg strength was used) and a meta-analysis of the data from two of these studies, including the study in which the 50 mg strength tablet was used.
The efficacy analysis will only consider the two clinical studies in which the pharmaceutical form and strength which obtained marketing authorisation were used (HRA2914-509 and HRA2914-513).

3.1. Efficacy

3.1.1 Study HRA2914-513

Method

Study design:
Randomised, single-blind study with two parallel groups comparing the efficacy and safety of ELLAONE with the efficacy and safety of levonorgestrel as emergency contraception within 120 hours after unprotected intercourse.

Primary objective:
to demonstrate that the pregnancy rate observed after taking ELLAONE within 72 hours of unprotected intercourse is significantly lower than the expected pregnancy rate in the absence of emergency contraception (the expected number of pregnancies was calculated on the basis of the probability of conception as a function of the cycle day)[1].

Secondary objectives:
- To demonstrate that the pregnancy rate observed after taking ELLAONE within 72 hours is significantly lower than 4% (clinical relevance threshold)[2].
- To demonstrate the non-inferiority of ELLAONE versus levonorgestrel if taken within 72 hours. Should non-inferiority be demonstrated, superiority will be tested.
- To demonstrate that the pregnancy rate when ELLAONE is taken within 120 hours is significantly lower than the expected rate in the absence of contraception.
- To demonstrate that the pregnancy rate observed after taking ELLAONE within 120 hours is significantly lower than 4% (clinical relevance threshold).
- To demonstrate the non-inferiority of ELLAONE versus levonorgestrel if taken within 120 hours. Should non-inferiority be demonstrated, superiority will be tested.

Endpoint:
Pregnancy test (diagnosed by urine test; if positive, confirmed by measurement of serum β-hCG levels).

Inclusion criteria:
- Women aged at least 16
- With regular cycles (24 to 35 days)
- Presenting for emergency contraception within 120 hours of unprotected intercourse, condom rupture or failure of another barrier method.
- Patients presenting more than 72 hours after unprotected intercourse were eligible only if fitting an IUD was contraindicated or refused.

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1 Trussell J, Rodriguez G, Ellertson C. New estimates of the effectiveness of the Yuzpe regimen of emergency contraception. Contraception. 1998;57(6):363-9.

2 The expected pregnancy rate in the absence of emergency contraception was estimated at 8% according to the conception probabilities supplied by Trussell *et al* (1998) and by earlier studies on emergency contraception (von Hertzen *et al* ,2002). A reduction of more than half in the pregnancy rate (i.e. 4%) is regarded as clinically relevant for emergency contraception.

Treatments:

- One 30-mg ELLAONE tablet (ulipristil acetate) or
- One 1.5 mg levonorgestrel tablet
- within 120 hours of unprotected intercourse.

Statistical method:

- The number of subjects necessary was calculated on the basis of the hypothesis that ELLAONE would not be inferior to levonorgestrel 1.5 mg taken within 72 hours, using the following criteria: power 85%, significance level = 5%, non-inferiority demonstrated if the upper limit of the 95% confidence interval of the odds ratio of the pregnancy rates in the ELLAONE group versus that in the levonorgestrel group was below 1.6 (equivalent to a non-inferiority margin of 1%, with the pregnancy rate after treatment with levonorgestrel being 1.7%).
  Assuming that contact would be lost with 10% of the participants, 910 patients needed to be recruited in each group.
- The primary aim was met if the upper limit of the 95% confidence interval of the pregnancy rate observed was below the expected pregnancy rate.
- Superiority versus levonorgestrel was demonstrated if the upper limit of the 95% confidence interval of the odds ratio of pregnancy rates in the ELLAONE group versus that in the levonorgestrel group was less than 1.

An interim analysis was scheduled to be performed on data from the first 1,200 patients treated within 72 hours of unprotected intercourse who met the modified intention to treat (mITT) criteria[3]. Recruitment would have to stop if the results of the statistical analysis for the primary efficacy endpoint, for the clinical relevance threshold and for non-inferiority were in favour of ELLAONE.
Under these conditions, the significance level was adjusted on the basis of this interim analysis.

Results

Population:

- 596 of the 1,200 patients meeting the mITT criteria in the interim analysis were treated with ELLAONE and 604 were given levonorgestrel 1.5 mg.
- In total 2,221 patients were recruited and treated: 1,104 in the ELLAONE group (of whom 941 as mITT) and 1,117 in the levonorgestrel group (of whom 958 as mITT).

Primary objective (interim mITT analysis based on the population treated within 72 hours):

- The pregnancy rate observed: 1.51% (95% CI [0.62; 3.32]) was significantly lower than the expected pregnancy rate: 5.63%.

Secondary objectives (interim mITT analysis based on the population treated within 72 hours):

- The upper limit of the 95% confidence interval of the pregnancy rate after treatment with ELLAONE was below 4%. The pregnancy rate after taking ELLAONE within 72 hours was therefore significantly below 4% (regarded as the clinical relevance threshold for emergency contraception).
- The odds ratio of pregnancy rates in the ELLAONE group versus that in the levonorgestrel group is 0.53 (95% CI [0.20; 1.44]). Its upper limit is therefore below the non-inferiority threshold (1.6).

3 Modified intention-to-treat population (mITT): patients had to meet the following criteria: have had the treatment; have had unprotected intercourse at least once during the current cycle prior to inclusion; for the result of the urine pregnancy test carried out after administration of the treatment to be known (contact with the patient maintained at this point); to be aged under 36; if pregnant, for this not to have been ascertained prior to administration of the treatment (serum ß-hCG levels and gestational age confirmed by echography) or considered "incompatible" with treatment failure (assessed by a Data and Safety Monitoring Board).

Secondary objectives (final mITT analysis based on the population treated within 120 hours):

- The pregnancy rate observed was 1.60% (95% CI [0.93; 2.67]); the upper limit of the confidence interval was below the expected pregnancy rate: 5.72%.

The main results of the study as a whole are shown in *table 1*.

Table 1: efficacy results for administration between 0 and 120 h, mITT analysis

	Pregnancy rate [95% CI] (n patients)		Odds ratio [95% CI]
	ELLAONE	Levonorgestrel	
0-72 h – interim analysis (n=1,200)	1.51% [0.62; 3.32] (n=596)	2.81% [1.54; 4.97] (n=604)	0.53% [0.20; 1.44]
0-72 h – final analysis (n=1,694)	1.78% [1.04; 2.98] (n=843)	2.59% [1.68; 3.94] (n=851)	0.68% [0.35; 1.31]
0-120 h – final analysis (n=1,893)	1.60% [0.93; 2.67] (n=939)	2.62% [1.75; 3.89] (n=954)	0.59% [0.31; 1.14]

3.1.2 Study HRA2914-509

Method

Study design:
Non-comparative prospective study

Primary objective:
To demonstrate that the pregnancy rate after taking ELLAONE between 48 and 120 hours after unprotected intercourse is significantly lower than the expected pregnancy rate in the absence of emergency contraception.

Secondary objectives:

- To demonstrate that the pregnancy rate observed after taking ELLAONE after between 48 and 120 hours is significantly lower than 4% (clinical relevance threshold).
- Analysis of pregnancy rates according to when ELLAONE is taken.

Endpoint:
Pregnancy test (diagnosed by urine test; if positive, confirmed by measurement of serum β-hCG levels).

Inclusion criteria:

- Women aged at least 18
- With regular cycles (24 to 35 days)
- Presenting for emergency contraception between 48 and 120 hours after unprotected intercourse, condom rupture or failure of another barrier method.

Treatment:
One 30-mg ELLAONE tablet (ulipristil acetate)

Statistical method

- The number of subjects necessary for analysis of the primary and secondary endpoints was calculated on the basis of the following hypotheses: power 80%; clinically relevant pregnancy rate after emergency contraception below 4%; pregnancy rate among patients receiving treatment (administration of ELLAONE within 48 to 120 hours) 2.5%.
  These criteria required 1,200 patients to be recruited for the upper limit of the 95% confidence interval of the pregnancy rate to be below 4%. Assuming that contact would not be maintained with 10% of participants, the number of subjects required was estimated at 1,320.
- The primary aim was met if the upper limit of the 95% confidence interval of the pregnancy rate observed was below the expected pregnancy rate (calculated on the basis of conception according to the cycle day).

An interim analysis was scheduled on the basis of data from the first 900 patients meeting the modified intention to treat (mITT) criteria[4] .
The significance level was adjusted for the interim and final analyses of the primary objective.

Results

Population:
In total 1,533 patients were treated and 1,241 were included in the modified intention to treat population.

Primary objective (mITT analysis)
The interim analysis of 900 patients found the pregnancy rate to be 2.22% [95% CI; 1.29-3.73], significantly below the expected pregnancy rate of 5.51%.
The final analysis demonstrated that the observed pregnancy rate of 2.10% (95% CI: 1.41%, 3.10%) was significantly lower than the expected pregnancy rate 5.53%.
Secondary objectives (mITT analysis)

- The upper limit of the 95% confidence interval of the pregnancy rate after treatment with ELLAONE was below 4% (considered as the clinical relevance threshold for emergency contraception).
- Pregnancy rates according to when ELLAONE was taken are shown in *table 2*.

Table 2: pregnancy rates according to when ELLAONE is taken.

Interval between intercourse and administration (hours)	48-72	73-96	97-120	Total (48-120)
n patients	693	390	158	1,241
n pregnancies	16	8	2	26
Pregnancy rate (%)	2.30	2.04	1.26	2.10

3.2. Adverse effects

3.2.1 Study HRA2914-513

A total of 2,221 patients were treated: 1,104 in the ELLAONE group and 1,117 in the levonorgestrel group. The most commonly observed adverse events are shown in *table 3*.

Table 3: most common adverse events

adverse events (% of patients)	ELLAONE (n=1,104)	Levonorgestrel (n=1,117)
headache	19.3	18.9
dysmenorrhoea	12.9	14.3
nausea	12.8	11.3
abdominal pain	5.1	6.7
vertigo	5.2	4.9
fatigue	5.5	3.9

The adverse events were regarded as treatment-related in 44.8% of cases after administration of ELLAONE and in 46.2% of cases after administration of levonorgestrel. The most commonly observed adverse effects are shown in *table 4*.

4 Modified intention-to-treat (mITT) population
Patients had to meet the following criteria:
Received treatment and had at least one unprotected intercourse reported at screening; Participated in the current study for the first time; Known pregnancy status using high sensitivity urinary pregnancy (HSUP) test after treatment intake; 35 years of age or younger; If pregnant, without pregnancy identified as having started before treatment intake (as measured by pre-treatment serum β-hCG level and gestational age confirmed by transvaginal ultrasound) or as “not compatible” with a treatment failure, based on independent evaluation (by a Data and Safety Monitoring Board).

Table 4: most common adverse effects

Adverse effects (% of patients)	ELLAONE (n=1,104)	Levonorgestrel (n=1,117)
Nausea	9.4	8.1
Headaches	8.4	7.5
Dysmenorrhoea	7.0	8.4
Vertigo	3.1	3.0

Seven serious adverse events were observed: three in the ELLAONE group and four in the levonorgestrel group. One serious adverse event was regarded as possibly being treatment-related in each group: vertigo in the ELLAONE group and molar pregnancy in the levonorgestrel group.

Effect on menstrual cycle
The average length of the cycle was 30.8 days in the ELLAONE group, i.e. an average increase of 2.1 days over the usual length. The average length of the cycle in the levonorgestrel group was 27.5 days, i.e. an average reduction of 1.2 days compared to the normal length.
Cycle length was altered by up to seven days in 82.5% of patients in the ELLAONE group and 90% of patients in the levonorgestrel group. It was altered by over 20 days in 2.7% of patients in the ELLAONE group and 1.2% of patients in the levonorgestrel group.
Intermenstrual bleeding occurred in 8.6% of patients in the ELLAONE group and 10.5% of patients in the levonorgestrel group.

3.2.2 Study HRA2914-509

A total of 1,533 patients received the treatment at least once during the study. One serious adverse event was observed. It was not regarded as treatment-related.
The most commonly observed adverse events are shown in *table 5*.

Table 5: most common adverse events

Adverse events (% of patients)	ELLAONE (n=1,533)
Headaches	17.5
Nausea	12.2
Abdominal pain	11.7
Dysmenorrhoea	6.7
Fatigue	5.6
Vertigo	5.4
Pelvic pain	3.8

The adverse events were regarded as treatment-related in 49.6% of cases. The most commonly observed adverse effects are shown in *table 6*.

Table 6: most common adverse effects

Adverse effects (% of patients)	ELLAONE (n=1,533)
Headaches	9.3%
Nausea	9.2%
Abdominal pain	6.8%
Dysmenorrhoea	4.1%
Vertigo	3.5%
Fatigue	3.4%

Effect on menstrual cycle
The average length of the cycle was 31.8 days, i.e. an average increase of 2.9 days over the usual length.
Cycle length was altered by up to seven days in 80.8% of the patients. It was altered by over 20 days in 5.1% of the patients.
8.7% of the patients experienced intermenstrual bleeding.

3.2.3 European risk management plan

The purpose of this plan is to collect data regarding the effect of ELLAONE on the progress of exposed pregnancies (which had not been identified at the time of administration or which result from treatment failure), the effect on the foetus, effects during lactation and off-label-use of the product. The plan includes:

- Setting up a regnancy register in order to collect all data related to the outcomes of pregnancies exposed to ELLAONE. The data will be analysed in the periodic safety update reports (PSUR). This register must start as soon as the medicinal product is launched.
- Peri-natal and post-natal toxicity studies in rats, with investigation into secretion in milk.
- A pharmacokinetic study in lactating women (depending on the results of the preceding study).
- An observational study as part of the Paediatric Investigational Plan to assess the safety of Ellaone among women aged under 18.
- Clinical follow-up of pregnancies in the practice among 1,000 targeted prescribers.
- Examination of prescription registries to identify off-label use.

3.3. Conclusion

In study HRA2914-513, the pregnancy rate among women taking ELLAONE was significantly lower than the expected pregnancy rate and below the threshold of 4% (regarded as clinically relevant for emergency contraception) for the time periods of 0 to 72 hours and 0 to 120 hours. This study concluded that ELLAONE is not inferior to levonorgestrel for the 0 to 72 hours and 0 to 120 hours time periods.

Study HRA2914-509, which did not include a comparison with a reference treatment, found a significant difference in favour of ELLAONE between the observed pregnancy rate and the expected pregnancy rate as well as between the observed pregnancy rate and the threshold value of 4%, when ELLAONE was taken between 48 and 120 hours after unprotected intercourse.
The adverse effects most frequently observed during the clinical studies were headaches, nausea, abdominal pain, dysmenorrhoea, vertigo and fatigue.

A European risk management plan has been set up. Its purpose is to collect data regarding the effect of ELLAONE on the progress of exposed pregnancies (which had not been identified at the time of administration or which result from treatment failure), the effect on the foetus, effects during lactation and off-label-use of the product.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

ELLAONE is intended for use as part of preventive therapy.
The efficacy/safety ratio is high.

Public health benefit

It is thought that one in three pregnancies in France is unwanted[5] and that around 200,000 abortions are performed each year[6].

In the light of this, and given the psychological consequences and associated social impact, the public health burden created by unwanted pregnancies and abortions can be regarded as high.

Ensuring access to suitable contraception, including emergency contraception, and reducing the rate of abortions (especially among young women), are public health objectives defined by the National Technical Group for Definition of Public Health Objectives.

There is a public health need, despite the widespread use of medicalised contraceptive methods[7], and this is confirmed by the steady rate of abortions carried out in recent years, with the rate rising among minors and women aged 18 to 19[5].

The response to this need requires better information about available methods of contraception and their use. Ellaone, an emergency contraception that can be used up to five days after high-risk intercourse, may offer a response to the identified public health need.

However, the fact that a prescription is required could impede access to Ellaone compared to Norlevo, especially for women under 19.

In view of the data available and the limits to the clinical trials submitted (only one trial in which Ellaone 30 mg was compared to an active comparator, multiplicity of criteria investigated), the product Ellaone is expected to have only a low theoretical impact.

However, it is not certain that these results can be transposed into practice, given the optimum conditions under which the women were managed in the context of the studies and the severely limited amount of data for women under 18.

Consequently, ELLAONE is expected to have a public health benefit. This benefit can only be low.

This medicinal product is intended for first-line therapy.

There are treatment alternatives (Norlevo 1.5 mg, Lévonorgestrel Biogaran 1.5 mg, copper IUD).

The actual benefit of this medicinal product is substantial.

5 Bajos N, Leridon H, Goulard H, Oustry P, Job-Spira N; COCON Group. Contraception: from accessibility to efficiency. Hum Reprod. 2003;18:994-9.

6 Vilain A. Les IVG en 2006. Etudes et résultats de la DREES n°659, septembre 2008.

7 Lydié N, Léon C. contraception, pilule du lendemain et interruption volontaire de grossesse. In guilbert P, Gautier A. Baromètre santé 2005. Premiers résultats : p 103-108

4.2. Improvement in actual benefit (IAB)

As ELLAONE has been shown to have statistically significant efficacy when measured against the threshold of 4% (regarded as clinically relevant for emergency contraception) and against the expected rate of pregnancies for the time period of 0 to 120 hours following unprotected intercourse or failure of a contraceptive method, ELLAONE offers a minor improvement in actual benefit (IAB IV) compared to NORLEVO.

4.3. Therapeutic use

4.3.1 Treatment strategy

Emergency contraception is a phrase describing the contraceptive methods which a woman can use to prevent becoming pregnant after having unprotected intercourse (no contraception or failure of a contraceptive method, such as condom rupture). It can take the form of a copper intrauterine device (IUD) or hormonal emergency contraception: levonorgestrel and now ulipristal.
Progestogen-based hormonal emergency contraception (levonorgestrel) is more effective the earlier it is taken after unprotected intercourse. Copper IUDs have a 0.1% to 0.2% failure rate when fitted after intercourse. They can be inserted up to five days after the estimated date of ovulation. A copper IUD is therefore the most effective method in the event of unprotected intercourse, but it is less accessible (has to be fitted by a medical practitioner) than levonorgestrel emergency contraception, which can be obtained from a pharmacy without a prescription and without the patient's identity being known (here it is free for minors who ask for it to be dispensed free of charge), in family planning centres or from school nurses[8].
ELLAONE can only be supplied with a doctor's prescription, which makes it less accessible than levonorgestrel emergency contraception.
Women using hormonal emergency contraception should be advised:

- to use an effective method of contraception (condoms) until the end of their current cycle;
- to have a pregnancy test if they do not have a period within five to seven days of the date they would expect their period to start, if they have abnormal bleeding on the date they would expect to have their period, or if they notice signs indicating that they might be pregnant;
- to regard hormonal emergency contraception only as a last bridging contraception method. The opportunistic and repeated use of hormonal emergency contraception as the only method of contraception is much less effective than a constant method, and is associated with a higher incidence of adverse effects, especially disturbance of the menstrual cycle (70% of cases). In the case of compliance problems, preference should be given to a constant method which is not subject to compliance variations (IUD, hormonal implants, etc.). Practitioners should discuss the relative advantages and disadvantages of constant and occasional methods with women who do not have intercourse regularly[8].

When prescribing and dispensing contraception, practitioners should give the woman preventive information on back-up contraception options if she has had unprotected intercourse, how effective they are and how she can access them. Similarly, when a practitioner is consulted by a woman or girl wishing to finding out about emergency contraception, or when a female patient mentions having had unprotected intercourse, not to have used her contraception properly, or states that she wants to take emergency contraception, the practitioner should inform the patient of the various back-up contraception options, how effective they are and the varying conditions governing access to them[8].

8 Afssaps – Anaes – Inpes. Clinical practice guidelines. How to choose a method of female contraception. December 2004.

As ELLAONE binds to progesterone receptors, it may reduce the efficacy of regular combination or progestin-only hormonal contraception. Consequently, women who have taken emergency contraception should use a reliable barrier method of contraception during subsequent intercourse until the start of their next period. ELLAONE should not be used more than once during a single menstrual cycle, or used together with levonorgestrel in the context of emergency contraception (see SPC).
In addition, the safety and efficacy of ELLAONE have only been established in women aged 18 years and older (see SPC). It is not recommended for use by women suffering from severe asthma which is not sufficiently controlled by an oral glucocorticoid.

4.4. Target population

The target population for emergency contraception is made up of all women of childbearing age who do not wish to become pregnant and who are at risk of becoming pregnant following unprotected intercourse as a result of failure of their usual method of contraception or because they did not use contraception.
210,000 abortions were performed in 2006. [9]
It is thought that six out of ten unintended pregnancies end in abortion[10]; this means that the annual number of unintended pregnancies in France would be around 350,000.
The likelihood of conceiving after unprotected intercourse is thought to be around 8%.
Consequently, the number of instances of unprotected intercourse each year would be around 4,400,000.
The annual target population for Ellaone would therefore be around 4,400,000 women.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication and at the posology in the marketing authorisation.

4.5.1 Packaging: Appropriate for the prescription conditions

4.5.2 Reimbursement rate: 65%

9 DREES – Studies and results n°659 – September 20 08.
10 Bajos N., Moreau C., *et al.* Why has the number of abortions not declined in France over the past 30 years ?- Populations et sociétés n°407- Decembe r 2004