EMERGENCY CONTRACEPTION

Position Paper on the Mechanism of Action

PREMISES

Italian Laws

Italian Laws direct conscientious birth control to the *safeguarding of the health of both the woman and the offspring since fertilization*. This is the article 1, comma 3, of the Law 405/1975. This protection is reaffirmed also in the Law194/1978 which, though allowing pregnancy termination in circumstances that should be exceptional, proclaims the safeguard of human life since its first beginning (beginning of human life, and not of "pregnancy" that the WHO, conventionally, considers starting with the embryo-implantation). The Law 40/2004, at last, in Assisted Reproduction Techniques (ART) procedures assures to the embryo the same protection guaranteed to his/her parents (a protection that has been never modified in the several corrections by the Constitutional Judges).

It is consequently important to know whether the drugs used in emergency contraception (EC), Levonorgestrel (LNG, Norlevo®) and Ulipristal Acetate (UPA, ellaOne®), do or do not prevent fertilization and, consequently, are or are not compatible with Italian Laws and, still more important, with the principles on which they are grounded.

The patients' informed consensus and the doctors' and chemist's professional freedom

Correct information on the mechanism of action (MOA) of these drugs seems then dutiful and is the essential requirement for the woman to express a fully free and informed consensus to use and for the doctors' decision to prescribe.

Several are the papers evidencing that the MOA is one of the main criteria on which is based any choice among the different contraceptives. [1-4] This is true for the women, the doctors and all the health-operators. The Italian Bioethics National Committee on July 12th 2012 acknowledged that the freedom of conscience is Constitutionally warranted to either the doctors and all the health-operators and it cannot leave a correct information apart.

DEFINITION

Emergency contraception is defined as the use of any drug, or the intrauterine insertion of devices, after unprotected intercourse with the aim of preventing an unwanted pregnancy. Unprotected

intercourse can lead to pregnancy only if it occurs in the fertile period of the cycle, that is, in the four-five days preceding ovulation and on the ovulation day itself. Only in these days, in fact, the cervical mucus allows the sperms to enter female internal genitalia. Among the fertile days, the pre-ovulatory day is the day on which the probability of conception is highest, followed by the ovulation day and by the second day preceding ovulation.[5-9] On these same days, the frequency of both protected and unprotected intercourse peaks.[6,10]

The use of EC is an attempt to prevent pregnancy that must face at least two facts. *The first one*: the sperms did already enter. Thanks to the fertile mucus they already passed through the cervical channel and many have already reached the tube;[11] there they await, resting, the oocyte release. No drug of the day-after can of course inhibit their ascent, given the fact it has already happened. *The second one*: ovulation is imminent.

At this point in time, everything in the female body is arranged for fertilization and for the subsequent embryo-implantation into the endometrium, which the luteal hormones will make hospitable after the ovulation.

Within this setting, a clinical appearance of pregnancy can only be avoided in two ways: by preventing ovulation *in extremis* and thereby preventing fertilization or by making sure that the embryo will not find the fertile ground he needs to implant within the uterus.

The substantial difference between the two hypotheses is evident: in the former fertilization is avoided, while in the latter the embryo is actively eliminated before he/she can implant and disclose his/her presence.

MECHANISM OF ACTION OF EMERGENCY CONTRACEPTIVES

The drugs currently used for EC are two: Levonorgestrel (LNG, Norlevo®), a potent synthetic progestogen, and Ulipristal Acetate (UPA, ellaOne®), a potent anti-progestagen quite similar to Mifepristone (RU486, Myfegyne®). The two drugs will be dealt with separately, while intrauterine devices will not be covered by this paper, as their MOA is clearly inhibiting the embryo-implantation, after fertilization.

It is important to note what is reported on ECs' MOA at the international level:

The producer (HRA Pharma),[12] the Food and Drugs Administration (US-FDA),[13] the European Medicines Agency (EMA),[14] the most highly reputed international and national gynecological Scientific Societies[15] report and affirm that ECs works by either inhibiting or delaying ovulation and therefore preventing fertilization without affecting implantation in any way.

Scientific and experimental evidence, on which this position paper is based, leads to a very different conclusion: in fact, these drugs consistently prevent fertilization only when they are

taken at the very beginning of the fertile period; in the subsequent fertile days, instead, and mainly in the days closest to follicular rupture, both ECs have no longer any effects on either ovulation or fertilization, while they transform the endometrium into an inhospitable environment for the embryo. Besides, the fertile days closer to ovulation are the most fertile ones in the menstrual cycle and are also the days in which, statistically, most intercourse and most fertilizations do occur.[5-7,12]

Unfortunately, it is hardly feasible to assess whether the woman is in her first fertile day or is closer to ovulation when she asks for the drug.

Most women ignore the signs of fertility, and the presence of semen within the vagina (that cannot be avoided following unprotected intercourse) can confuse the search and the observation of the cervical mucus. Moreover, the levels of LH, the hormone that leads to follicular rupture, cannot indicate exactly how far the next ovulation is. Low levels should indicate that ovulation is far, but LH levels might start rising just after the blood drawing as they can vary rapidly at that time.

The regulation of these events is highly complex and several important mechanisms are still to be understood.

Even the ultrasound measurement of the diameter of the dominant follicle, the follicle that is going to release the oocyte, cannot provide a valid indication on when it will rupture. Only a diameter of 12-14 mm places the woman at the border between the infertile and the fertile days,[16] suggesting that intercourse in the previous days could hardly end in fertilization. Whenever the follicle is larger, it would be impossible to foresee the ovulation time, given the high variability of these events between women. The ultrasound measurement of the endometrial thickness, in turn, seems unable to discriminate by a cut-off value the probability of conception in the overall fertile period.

Given the premises, the evaluation of the two types of EC Pills and of their MOA will be detailed.

- ***LEVONORGESTREL (LNG, Norlevo®)***

Each tablet of Norlevo® contains Levonorgestrel 1.5 mg, to be taken in a single oral dose. The drug is presented as an emergency contraceptive to be used within 72 hours since unprotected intercourse,[17,18] clearly occurred in one of the pre-ovulatory fertile days. However, the treatment efficacy seems to persist up to 96 hours without any significant reduction.[18]

Anti-ovulatory effects

LNG is reported to delay or inhibit ovulation and consequently to prevent fertilization without affecting embryo-implantation in any way.

This is stated by the International Consortium for Emergency Contraception (ICEC) and the International Federation of Gynecology & Obstetrics (FIGO) in their 2008, 2011 and 2012 joint

Statements "How do Levonorgestrel-only emergency contraceptive pills (LNG-ECPs) work to prevent pregnancy?".[15]

Actually, in the studies quoted in support to the Statements,[15,19-23] ovulation is not inhibited when LNG is taken in the advanced pre-ovulatory phase, a phase that encompasses the most fertile days of the cycle. A delay in ovulation can only be observed, however only in 80% of the treated women and not in all of them, when LNG is taken in the first fertile day and that is 4-5 days before ovulation.

Of course, a woman taking the drug in the first fertile day, following unprotected intercourse occurred one to three days earlier, would likely take the drug unnecessarily, as that intercourse likely occurred in a still infertile period.

The above quoted studies,[15,19-23] besides evidencing that most women do ovulate regularly when LNG is taken in the pre-ovulatory fertile period, show that in those same women LNG prevents the formation of an adequate corpus luteum.[20-23] The drug impairs the production of those hormones (Progesterone above all) that shall prepare the endometrium to embryo-implantation, leading to the impossibility for the embryo to implant.

It must be stressed that LNG taken in any of the fertile days is, nonetheless, highly effective: it prevents the clinical appearance of 70% of pregnancies,[24] though it is unable to prevent ovulation. In a recent study, in particular,[25] ovulation was observed in 66% (57 out of 87 total cases) of patients treated with LNG in the fertile pre-ovulatory phase; in 79% (57 out of 72 evaluable cases) if the 15 patients are excluded which were lost to the follow-up. Ovulation occurred, but no clinically evident pregnancies were observed out of the 13 expected.

Evidently, Norlevo effectiveness, that is the ratio between observed and expected pregnancies, must be due to something else, namely, to the alterations in the endometrial tissue.

Cohort studies[26,27] further confirm this suggestion, as they clearly evidence that it is exactly the pre-ovulatory administration of LNG that prevents the clinical appearance of pregnancies. Due to the fact that once ovulation occurs fertilization can normally follow, the contraceptive effect must necessarily be a post-fertilization one.

Endometrial effects

FIGO Experts, affirm that Levonorgestrel does not prevent nidation and they repeat this in all the three subsequent Statement editions.[15] In support of this they report two studies which use cultures of endometrial tissue obtained from fertile women with normal cycles, who had received no hormonal treatment.[28,29]

In particular, in the two studies, they use cultures of luteal endometrium obtained five days after ovulation, that is when its receptivity is highest. Embryos are placed in this absolutely hospitable

endometrium. In the presence of Progesterone 10 embryos out of 17 do attach (57%), while in the presence of LNG the percentage of attachments is lower: 6 out of 14 succeed (43%). The difference is presented as not significant, even if the number of cases is quite insufficient to allow such a conclusion.

However, even accepting that Levonorgestrel, added in the culture, cannot inhibit human blastocyst attachment, it must be stressed that these studies use quite normal luteal endometrial tissue obtained from patients who had not been pre-treated with any hormonal treatment; these studies do not use endometrium obtained from women given Levonorgestrel in the pre-ovulatory fertile days. These studies allow to say just one thing: that Levonorgestrel, taken five days after fertilization, during a normal luteal phase, cannot impair an embryo-implantation already in progress; but surely these are not the days in which emergency contraceptives are usually recommended.[30,31]

At this point a further information is dutiful to qualify the reliability of FIGO e ICEC joint Statements.[32]

The Statements' authors - Brache, Faundes, Fraser (gynecologists) and Trussell (statistician) - are reported in the official website of the European Society of Contraception and Reproductive Health (http://www.escrh.eu/about-esc/news/how-do-levonorgestrel),[33] where they are thanked "*for their incredible attention to detail and persistence in making sure this statement was accurate and fully reflected the most recent studies*".

Brache is the first author of a paper on ellaOne® (UPA) supported by HRA Pharma.[34] At the end of the paper she compares the anti-ovulatory efficacy of UPA and LNG and concludes that the combined evaluation of data from two similar trials "*resulted in follicle rupture inhibition in 7/48women (14.6%) of the LNG studied cycles*" in the advanced follicular phase.

The quoted trials are two studies where she and Faundes stress that LNG is not able to inhibit ovulation in the most fertile days of the cycle[35, 36] and this conclusion is reaffirmed, even recently, in a further paper where she compares different ECs. [37] In the Statements, on the contrary, Brache and Faundes – in sync with the other two FIGO Experts – do state exactly the opposite of what is evident in their own studies. On behalf of all the world gynecologists (FIGO), they state officially and dogmatically "*that inhibition or delay of ovulation is LNG ECPs' principal and possibly only mechanism of action*".

This Statement appears as the official Truth, unanimously shared by all the world gynecologists. On it the doctors will base their professional and ethical choices. On it the women will base their personal choices, believing that LNG does prevent fertilization. On it the Nations and Governments will rely when they will legislate on these vital topics.

- ***ULIPRISTAL ACETATE (UPA, ellaOne®)***

Each tablet of ellaOne® contains 30 mg of micronised Ulipristal Acetate, to be taken in a single oral dose. It is unanimously acknowledged that 30 mg of micronised UPA are equivalent to 50 mg of unmicronised UPA, the drug used in previous clinical trials that was administered in gelatin capsules.[12,38]

The producer, HRA Pharma, affirms that ellaOne®, administered in the fertile period of the menstrual cycle, is able to delay ovulation and prevents the entrance of the spermatozoon into the oocyte. EllaOne® would be able to postpone follicular rupture up to five days even when taken immediately before ovulation is scheduled to occur and its efficacy would be consistently high even when the drug is taken up to five days after unprotected intercourse.[12]

This statement, based on the above mentioned Brache's paper,[34] is fully endorsed and shared by ICEC e FIGO (http://sigo.it/pdf/medical_service_delivery_guidelines.pdf).[39]

It must be reminded that fertilization can occur only when intercourse do occur in the 4-5 pre-ovulatory days in which the cervical mucus allows the sperm to enter female genitalia and that it usually occurs within 24 hours since ovulation.

In the fertile days, at the ovarian and pituitary levels, several events can be observed that prepare ovulation and lead to follicular rupture: the increase in estrogen levels (which immediately starts making the cervical mucus fluid) leads to a progressive increase in LH levels (LH surge) which, in turn, reach their peak levels that are maintained even for hours. Ovulation normally occurs 24-48 after the LH peak, but can occur also later.[8]

If these events are put on a chart representing the fertile days of the menstrual cycle, it is easy to realize that the period preceding the LH surge coincides with the beginning of the fertile period; the one in which LH levels rise coincides with the second-third fertile days; while the days of LH peak (24-48 pre-ovulatory hours) and the following day, that in which ovulation occurs, are the last fertile days, the most fertile ones of the menstrual cycle.

Anti-ovulatory effects

Only one study evaluates the effects of Ella(One)® on ovulation when it is taken in the different days of the fertile period. It is the study by Vivian Brache, already mentioned. The authors suggest that UPA is able to inhibit or significantly delay follicular rupture for over 5 days, even when it is administered immediately before ovulation,[34] a point that is emphasized in the title, in the abstract and in the paper conclusions.

The number of the study-subjects is small: 34. At first they are evaluated as a whole and then separately, stratified into three groups according to whether they took Ulipristal before LH levels starts to increase, or during LH surge, or later when the LH peak levels are reached.

The first overall evaluation evidences that ellaOne® taken in the fertile period of the cycle inhibits or delays ovulation in 58.8% of the women. This means that 41.2% of the women treated in the fertile period do ovulate regularly and fertilization can occur.

However, the effects of UPA are reported to be highly dependent on the levels of luteinizing hormone (LH) at the time of administration. Only in the eight women treated at the beginning of the period one can observe a consistent delay in ovulation. This effect starts to decrease when the drug is administered during the LH surge: in these circumstances results show that ovulation is delayed in 78.6% of cases (in eleven women out of fourteen, while three women do ovulate and fertilization can follow). What is most striking to note is that in the patients treated at the LH peak ovulation is delayed in only one woman out of twelve: 92% of women do ovulate and fertilization can follow.

Moreover, in the results section, the authors state that when UPA is taken at the LH peak, one-two days before follicular rupture, the drug has no ability to either avoid or delay ovulation and behaves exactly like a placebo ["*when UPA was given at the time of the LH peak, the time elapsed to rupture was similar to placebo (1.54±0.52 days versus 1.31±0.48 days)*."]. These days are known to be the most fertile in the cycle, those in which most fertilizations do occur; those days in which a drug with a steadily high contraceptive efficacy, which is consistently above 80%, should prevent ovulation with the highest efficacy if its efficacy were due to an anti-ovulatory effect.

UPA ability to delay ovulation is highest (100%) only at the start of the fertile period; thereafter it decreases sharply and quickly and becomes almost null (8%) in the two pre-ovulatory days. In spite of this, its effectiveness in preventing pregnancies is very high (≥80%) and does not decrease depending on which of the five days it is taken on, after unprotected intercourse.[38,40-42] This appears surprising if UPA effectiveness was assumed to be due to an anti-ovulatory action, as its effect on ovulation decreases sharply as LH levels approach the peak. A progressive reduction in its effectiveness should be expected as the pre-ovulatory days elapse. On the contrary, its efficacy remains very high.[32,43]

It can be concluded that when ellaOne® is taken in the most fertile days of the cycle, that is one-two days before ovulation, it does not exhibit any anti-ovulatory MOA.

This points out that the contraceptive MOA must be due to something else and particularly to its inhibitory endometrial effects.

One again, before entering into the details of the endometrial effects, it is worth looking at the inconsistency of some information delivered by authors coming from renowned scientific institutions.[44,45]

Recalling Brache's statement on ellaOne®, "*when UPA was given at the time of the LH peak, the time elapsed to rupture was similar to placebo (1.54±0.52 days versus 1.31±0.48 days)*". It means that UPA behaves exactly like a placebo when it is taken at the LH peak.

Neither ellaOne®, nor, evidently, the placebo, when administered at the LH peak have any effects on ovulation, which occurs physiologically one-two days later.

Contrary to this scientific evidence, Gemzell-Danielsson and Lalitkumar, in two 2013 papers, respectively at the pages 302[44] e 93[45], detail verbatim: "*Even on the day of the LH peak, UPA could delay ovulation for 24 to 48 h after administration*". They state that UPA would be effective and able to delay ovulation even at that point, while it is proven that it is ineffective like the placebo. In both papers appears the same sentence, supported by the prestige of a renowned Institute.

Endometrial effects

Let's come to the endometrium. One single dose of Ulipristal Acetate modifies deeply endometrial receptivity at whichever time it is given: both in the mid-follicular phase, before the beginning of the fertile days;[46] and at mid-cycle in the days that follow ovulation (and the eventual fertilization);[47] and also in the mid-luteal phase,[48] which are precisely the days in which the embryo would implant. Under the effect of this drug, the pro-gestational effects of Progesterone on the endometrium are lost and, among them, the expression of those proteins that make the maternal uterus hospitable for the embryo. These effects are just identical to those observed after the administration of Mifepristone (RU486), but UPA is effective even at lower doses.[32]

Endometrial inhibition is direct and is due to the inhibition of endometrial Progesterone receptors (the same MOA of the pill RU486).[49-54] Essentially, ellaOne® occupies those cell structures to which Progesterone must necessarily link in order to perform its pro-gestation functions. Progesterone is present but cannot act and the endometrium will not transform into a hospitable ground.

Such inhibition is observed even after the administration of UPA at doses which are much lower – even five times lower – than those in ellaOne®. It is well documented that the threshold for altering endometrial morphology is lower than that required for altering folliculogenesis.[46-48] EllaOne®, consequently, will lead consistently to an inhospitable endometrium and whenever fertilization will occur the embryo, inevitably, will not be allowed to implant and survive.

In summary, the women who take Ulipristal after unprotected intercourse in the fertile days mostly do ovulate and fertilization can follow. The sperms, at that point, will be already inside the tube and the oocyte is released: nothing can prevent fertilization. Unfortunately, the endometrium is irreversibly damaged, independently of the period when UPA is taken.

On the other hand, the great and advertised innovation about ellaOne®, presented as "five days-after pill", is that it is quite effective even when taken up to five days after intercourse occurred in the fertile period. It is acknowledged that the pre-ovulatory day is the most fertile one. In case of unprotected intercourse in that day, with ovulation within the next 24 hours, fertilization would occur within 24 further hours, which would mean within 48 hours since intercourse. EllaOne® can be taken with an unchanged and consistently high efficacy up to five days since that intercourse, that is up to four days after ovulation and up to three days after fertilization. How can any anti-ovulatory or anti-fertilization MOA be used to explain this consistent and high efficacy? The only possible MOA is anti-implantation.[32,43]

It is evident that these drugs mostly prevent the embryo-implantation. This mode of effect, which is the opposite of what is officially communicated, is not compatible with the respect of human life since its first beginning in the form of an embryo, as the existing embryo is not allowed to implant following the drugs intake.

Furthermore, deceptive information is found in medical literature even in relation to UPA endometrial effects and, again, by the same author.

In a 2013 paper,[55] at the page 5, discussing the endometrial effects of UPA given in the early luteal phase, that is after the eventual fertilization, Gemzell-Danielsson reports that unmicronised UPA, at the doses of 50 and 100 mg, leads to a reduction in endometrial thickness and to an increase in endometrial Progesterone receptors (which means a lack of Progesterone action), effects that make the embryo-implantation impossible. These are exactly the data from Pamela Stratton.[47] At the same time, however, Gemzell-Danielsson adds that the dose used for EC cannot affect the endometrium. She details verbatim: "*Yet, in the doses relevant for EC use (30 mg) UPA has no significant effect on the endometrium*". She seems to forget that ellaOne®, 30 mg of micronised UPA, is quite equivalent to the 50 mg of unmicronised UPA [12,40] which were administered in Stratton's study and, consequently, must necessarily have the same anti-implantation effects on the endometrium. But what is most surprising, in this sequence, is that in the same paper, at the page 9, Gemzell-Danielsson herself reports, and acknowledges, that 30 mg of micronised UPA (ellaOne®) are quite equivalent to 50 mg of unmicronised UPA.

The same unfair sentence is repeated by the same author in a 2014 Review,[56] in the first paragraph of page 687 where she details verbatim that "*UPA given in early-luteal phase shows dose-dependent effects with no significant endometrial effects observed following exposure to doses relevant for EC*".

However, the lines which follow seem still more worrisome: there she quotes Lalitkumar [29] – a paper already mentioned in this position paper [28] of which she is the last author – and details verbatim:

"*To be able to study the effect of EC on human implantation, an in vitro three-dimensional implantation model has been developed. In this model it has been demonstrated that LNG or UPA at EC concentrations have no effect on the human embryos or endometrial receptivity and cannot impair or prevent implantation* [29]".

In the quoted paper, however, Ulipristal is never mentioned at all. UPA has not been tested in any way in that study and does not appear in any point of it.

Even with the greatest goodwill, the above behavior seems inexcusable.

Even the substance of the message is quite deceiving and sharply clashes with the scientific evidence: in that study,[28] in fact, Mifepristone (RU486), the molecule which is extremely similar to UPA as to its chemical structure and biologic activity, does prevent the attachment of all the embryos consistently. Ulipristal and Mifepristone share the same MOA but UPA is effective at even lower doses.[32,46-48]

The deceiving choice of omitting the truth, however, is not a peculiarity of the above mentioned authors: unfortunately, it concerns also the European Medicines Agency, EMA, the Agency that should be the endorser of the scientific truth and of the information correctness towards the doctors and, first of all, towards the people.

In the recent document "*Levonorgestrel and Ulipristal remain suitable emergency contraceptives for all women, regardless of bodyweight*" (EMA/631408/2014),[57] released by EMA on September 30th 2014 at the conclusion of the "Article 31 referral procedure" regarding the efficacy of ECs in overweight women, it has been reaffirmed that anti-ovulatory effect is the only MOA for ECs. In that document, at the end of the "*Information to healthcare professionals*", six references are quoted. The last one recalls – and makes it extant – the previous EMA document: "*CHMP Assessment Report for Ellaone*" (EMEA-261787-2009),[58] the one that led to ellaOne® Marketing Authorisation. From that document it is evident that EMA acknowledges very well that:

1. "*Ulipristal acetate prevents progesterone from occupying its receptor, thus the gene transcription normally turned on by progesterone is blocked, and the proteins necessary to begin and maintain pregnancy are not synthesized.*" This is reported under the title "non-clinical aspects" (page 8).
2. The efficacy of Ulipristal Acetate (UPA) and the efficacy of Mifepristone (RU486) in terminating pregnancy in primates are quite equivalent (page 10).
3. In emergency contraception "*alterations to the endometrium may also contribute to the efficacy of the product*", therefore acknowledging a post-fertilization MOA that is never mentioned in the package leaflet of ellaOne® (page 23).
   Besides, it is reported verbatim that "*The dose of 50 mg unmicronized ulipristal acetate was chosen in the phase II studies, since this was the minimal dose that alters endometrial maturation and induces inhibition of ovulation.*" (at the end of page 22).

4. The possibility that UPA is used *off-label* for pregnancy termination is real and is presented as a "safety concern" in the Table "Summary of the risk management plan for Ellaone" (page 41- second box on the left), but the strategic choice for the "proposed risk minimization" has been "*Omit any sentence in the SPC and the PL suggesting that the product could be used as an abortifacient."* (page 41 - second box on the right).
   At last, EMA and HRA Pharma agree that all of the approaches to avoid this abuse suffer from inevitable limitations; the only way may be prescription registries (page 45 and 46) (*the prescriptions that EMA now wants to abolish*).

Based on the review of the whole document (*CHMP Assessment Report for Ellaone*) the EMA-CHMP recommended the granting of the marketing authorization with the indication of emergency contraception. EllaOne® was marketed in Europe as an anti-ovulatory drug with the consent of each single National Medicines Agency.

No new data did appear in the medical literature on the endometrial effects of Ulipristal: the papers that describe them in the above EMA document are the same quoted in the present Position Paper: HRA2914-505*: Stratton.*[46] HRA2914-506: *Stratton.* [47] HRA2914-503: *Passaro.*[48] They are the same [47] that were distorted by Gemzell-Danielsson in 2013 and 2014. [55,56]

At last, in the above mentioned document "*EMA Annex I – Summary of Product Characteristics*" up-dated September 2014,[14] at page 7, point 5.1 – *Pharmacodynamic properties*, is detailed verbatim: "*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*."

"in some women": in 8% of women as Brache reports.[34]

In spite of this and of the just recalled evidences,[58] the package leaflet at page 20, point 1, reports verbatim "*ellaOne is thought to work by stopping your ovaries from releasing an egg*".[14]

This appears, again, contrasting with the scientific evidence.

It seems reasonable to assume that EMA was well aware of UPA's prevalent post-fertilization effect and, furthermore, of its ability to terminate pregnancy with the same efficacy of Mifepristone (RU486), when it chose to present UPA as an anti-ovulatory drug.

At last, in the Assessment Report EMA/73099/2015 concluding the EMEA/H/C/001027/II/0021 Procedure (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/001027/WC500181904.pdf) EMA acknowledges that "*on the day of the LH peak ulipristal acetate, similar to levonorgestrel, cannot delay or inhibit ovulation any better than placebo*" (page 67). As well, in the table summarizing safety Concerns, the "*Effects on pregnancy maintenance/off label use*" are reported again as important potential risks (page 63 - first line). In spite of this, the EMA-CHMP agreed with the removal of "pregnancy" as a contraindication and

changed ellaOne prescription status to "*medicinal product not subject to medical prescription*" in the EU.

Ulipristal and Mifepristone: the twin molecules

Ulipristal e Mifepristone share many effects in the female reproductive apparatus.[17,32,59-63]

Mifepristone is largely used and highly effective for EC in China, at doses of 25-50 mg.[17] When it is taken in the follicular phase, before the beginning of the fertile period, its effects on ovulation are similar to those of UPA,[64] though UPA is effective at much lower doses.[46]

As well, when administered in the early luteal phase, 200 mg dose of mifepristone is highly effective in preventing the clinical appearance of pregnancy.[65-67] Ovulation and fertilization, of course, would already have occurred at that point. These effects are the same observed with lower doses of UPA.[47]

Lastly, when administered in the mid-luteal phase, both Mifepristone and unmicronised Ulipristal, at the same dose of 200 mg, consistently induce a premature endometrial bleeding.[48]

Mifepristone (RU486) 200 mg is the drug administered for pregnancy termination.

Ulipristal has never been tested for pregnancy termination in women. Nonetheless, UPA and RU486 share the same effects on either folliculogenesis and endometrial differentiation, at doses that are quite the same.[51-54] Besides, both Ulipristal[68,69] and Mifepristone,[70,71] always at the same doses (5 mg daily for three months), are able to decrease fibroid size and reduce the intensity of uterine hemorrhage.

Currently, micronised UPA has been licensed, in Western Europe, for fibroid reduction prior to surgery. It is marketed as Esmya®, 5-mg tablets in a blister pack of 28 tablets for a total amount of 140 mg (ellaOne® contains 30 mg).

It seems important, here, to remind that 120 mg of micronised UPA (a dose which is lower than the amount in Esmya® and that can be obtained with only four tablets of ellaOne®) are equivalent to 200 mg of unmicronised UPA[40], which, in turn are equivalent to 200 mg of Mifepristone: the dose used to terminate pregnancies. Both the drugs, at these doses, taken seven days after ovulation and fertilization, exactly in the days when the embryo becomes implanted, consistently lead to a premature uterine bleeding.[48,72]

This should be carefully considered when deciding the prescription rules and limitations of any UPA-containing drug.[32]

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