A single dose of ulipristal acetate (UPA) 30 mg has recently been approved for emergency contraception (EC) up to 120 h after unprotected intercourse. A meta-analysis of clinical trials comparing UPA with levonorgestrel (LNG) for EC demonstrated that UPA has higher efficacy. Both treatments have similar side effects. The mechanism of action of both LNG and UPA for EC is by delaying or inhibiting ovulation. However, UPA appears to have a direct inhibitory effect on follicular rupture that allows it to be effective even when administered shortly before ovulation, a time period when LNG is no longer effective. This article summarizes clinical data available on UPA for EC and provides evidence that UPA, a second-generation progesterone-receptor modulator, represents a new effective alternative for EC.

Keywords: ellaOne®/Ella® • emergency contraception • selective progesterone-receptor modulator • ulipristal acetate

Emergency contraception (EC) is defined as the use of any drug or device, used after unprotected intercourse to prevent an unwanted pregnancy. EC offers a second chance to prevent pregnancy when contraception has failed or no method has been used. Recently, a new hormonal method of EC has become available, which is a progesterone-receptor modulator known as ulipristal acetate (UPA). It is a drug designed and developed specifically for that purpose, with a more potent mechanism of action than previous methods, promising better efficacy and a wider time window for use. A single dose of UPA 30 mg has recently been approved for EC use up to 5 days after unprotected intercourse (compared with 3 days for existing oral EC). This extended timeframe of use will thus allow more women who have had unprotected intercourse the opportunity to have an orally effective EC method. The objective of this article is to give an overview of the clinical data on this new option for EC.

Development of emergency contraception

Methods used postcoitally have included stilbestrol, ethinyl estradiol and levonorgestrel (LNG), danazol and mifepristone [1–4], or insertion of a copper intrauterine device (IUD) [5]. The hormonal methods are usually considered to be more convenient than the insertion of a copper IUD, which is otherwise the most effective method. In the late 1970s, Yuzpe introduced a regimen consisting of ethinylestradiol 0.1 mg and LNG 0.5 mg, given within 72 h of the intercourse and repeated after 12 h [6]. The Yuzpe regimen remained the standard hormonal EC method until the introduction of treatment with LNG only, or mifepristone, which were shown to be associated with less side-effects and higher efficacy than the Yuzpe regimen [7,8]. Mifepristone is currently only used clinically for EC in China and Russia.

Recently, a new class of a second-generation, selective, progesterone-receptor modulator (SPRM), known as UPA, has been developed and approved for EC treatment for use up to 5 days after sex (a timespan that corresponds to the lifespan of follicular rupture).
sperm in the reproductive tract). A single dose of UPA 30 mg for EC (ellaOne®, HRA-Pharma, Paris, France) was approved by the EMA in May 2009 and by the US FDA in June 2010 (Ella®).

**Ulipristal acetate**

Ulipristal acetate is a SPRM that is a derivative of 19-norprogesterone and was developed to have enhanced specificity for the progesterone receptor (Figure 1). The pharmacodynamic properties of UPA in humans reflect the mixed progesterone agonistic/antagonistic profile of the molecule [9]. UPA is the first SPRM approved for EC (ellaOne or Ella). The half-life of UPA after oral intake is 32.4 h [101]. Of the administered 97–99.5% of UPA, binds to plasma proteins in the blood, and it is mainly metabolized by cytochrome P450 (CYP3A4). Following oral administration of a single 30 mg dose, UPA is rapidly absorbed, with peak plasma concentrations occurring approximately 0.5–3 h after ingestion depending on whether the drug is taken during the fasting state or after a meal. It is recommended that if vomiting occurs within 3 h of UPA intake, then another tablet should be taken [9].

*In vitro* studies have shown that CYP3A4 is primarily responsible for the metabolism of UPA [9]. Although specific drug–drug interaction studies have not been performed, it is possible that inducers of CYP3A4, for example, rifampin, dexamethasone, St John’s Wort and certain anticonvulsants (phenytoin, phenobarbital and carbamazepine), may induce the metabolism of UPA and cause lowered plasma levels. Furthermore, inhibitors of CYP3A4, for example, the HIV-protease inhibitors, itraconazole, erythromycin and grapefruit juice, may inhibit the metabolism of UPA and cause increased plasma levels [9].

**Mechanisms of action of ECP**

Both UPA and LNG have been shown to be able to delay ovulation, although the effective time window for LNG for EC is rather narrow. It begins after selection of the dominant follicle, but ends before luteinizing hormone (LH) begins to rise. LNG, if taken when LH has already started to rise, cannot prevent ovulation and has no effect on the endometrium or other post-ovulatory events, and is thus ineffective at preventing pregnancy [10,11]. This is supported by clinical data on women exposed to unprotected intercourse at the time of ovulation [12]. In a series of clinical trials, the effect of UPA at different follicular diameters and in relation to the LH peak and ovulation was studied [13]. When given prior to the LH rise, UPA inhibited 100% of follicular ruptures. When UPA was administered when the size of the leading follicle was 18 mm (ovulation imminent), follicular rupture failed to occur within 5 days following treatment in 59% of women [14]. In contrast, a similar study using the EC dose of LNG at this phase of the cycle showed that ovulation was delayed by 5 days in only 12% of subjects, which was no better than placebo [15]. This demonstrates that UPA is a more potent inhibitor of ovulation at a time in the cycle when the risk of pregnancy is greatest.

The effect of UPA on the endometrium has been demonstrated to be dose dependent. When a single dose of UPA (10, 50 or 100 mg) or placebo was given just after ovulation, there was a decrease in endometrial thickness and an inhibition of downregulation of progesterone receptors with UPA compared with placebo [16]. However, on histological dating, a delay in endometrial maturation was only observed at the highest dose of UPA (100 mg); while the effect of lower doses of UPA equivalent to the 30 mg used for EC were similar to that of placebo. This might suggest that the EC dose of UPA may not exert antifertility effects on the endometrium [16].

Since the main action of UPA for EC is to delay ovulation, it is important that further acts of unprotected sex during that same cycle should be avoided in order to avoid pregnancy at the time of postponed ovulation.

**Efficacy of UPA: clinical trials**

To date, there have been two randomized controlled trials (RCTs) comparing UPA and LNG as a method of EC. Both studies were of similar design (noninferiority) and recruited women with regular menstrual cycles who were not using hormonal contraception, not breastfeeding, not using an IUD and not sterilized. The first study was conducted in the USA and recruited 1672 women who presented within 72 h of unprotected intercourse to receive either UPA (50 mg capsule) or LNG (1.5 mg taken as two separate 0.75 mg doses 12 h apart) [17]. In this study, the pregnancy rates with UPA were less than 1% and with LNG were 1.7%. This difference was not statistically significant but demonstrated that UPA was as least as effective as LNG. The second RCT was conducted in both Europe and the USA and recruited 2221 women presenting within 120 h of unprotected sex. In this study, women were randomized to receive either UPA (30 mg micronized tablet) or LNG (single 1.5 mg dose) [18]. The 30 mg micronized UPA tablet was specifically developed to reproduce the pharmacokinetic profile of the 50 mg capsule. Pregnancy rates were 1.6% amongst women who received UPA and 2.6% amongst...
those receiving LNG. Statistically, this difference in pregnancy rates was not significant. However, when pregnancy prevention rate was calculated (based upon conception probabilities according to cycle day of intercourse), then UPA was shown to prevent significantly more pregnancies than UPA \((p = 0.037)\).

A further noncomparative study using UPA (30 mg micronized) was conducted in the USA and examined use of UPA for EC in 1241 women presenting between 48 and 120 h after EC. In this study, a pregnancy rate of 2.1% was observed, which was significantly less than the 5.5% pregnancy rate that would have been expected in the absence of EC \([19]\). This study also showed that efficacy of UPA did not decrease with time; pregnancy rates were 2.3, 2.1 and 1.3% for EC intake 48–72 h, 72–96 h and 96–120 h, respectively, after sex \([19]\).

In order to increase statistical power to detect any difference in efficacy between UPA and LNG, data from both RCTs that compared UPA and LNG for EC were combined in a meta-analysis \([18]\). This meta-analysis contained data on 3445 women and showed that for those treated with UPA, the risk of pregnancy was significantly reduced compared with those who received LNG. For women who were treated with UPA within 72 h of unprotected intercourse, the risk of pregnancy was almost half of those receiving LNG \(\text{(Table 1)}\). Furthermore, if EC was taken within 24 h of intercourse, the risk of pregnancy in women who received UPA was reduced by almost two-thirds that of women receiving LNG \(\text{(Table 1)}\).

A cost–effectiveness analysis comparing UPA and LNG for preventing pregnancy has been conducted using the efficacy data from this meta-analysis and using published healthcare costs from the UK in 2008–2009 for treating women for an unintended pregnancy \(\text{(induced abortion and delivering a baby)}\) \([18]\). This analysis calculated that the monetary cost of preventing one additional unintended pregnancy by using UPA rather than LNG was GB£311, which was significantly cheaper to the health service than the cost of either an abortion (GB£672) or childbirth (GB£2380) \([20]\).

### Bleeding profiles & adverse events

On average, the dose of UPA used for EC (ellaOne or Ella) tends to lengthen the menstrual cycle by approximately 1–2 days \([9,17–19]\). However, the amount of delay varies with the dose used and the time of administration in the menstrual cycle, with the least effect occurring at approximately mid-cycle \([9]\). There is no difference in the volume or duration of menses after treatment with UPA for EC \([18]\).

Over 4000 women have been exposed to UPA in all the clinical trials to date and the side-effect profile of UPA seems similar to that of LNG \([17,18]\). The commonest reported adverse effects for both UPA and LNG in the largest comparative study were headache \((19\%)\), followed by dysmenorrhea and nausea \(\text{(Figure 2)}\) \([18]\).

### Interactions

Since UPA is a SPRM, there are concerns that it could alter the effectiveness of progestogen-containing hormonal contraception. Studies to examine the combined effects of UPA and progestogen-only or combined hormonal contraception have not yet been conducted. There are data from other SPRMs showing that supplementary administration of a SPRM improved bleeding patterns in women using a progestogen-only pill and subdermal contraceptive implants releasing LNG (Norplant) \([21,22]\). The improvement in bleeding pattern could be either a direct effect of the SPRM on the endometrium, or by inducing ovulation \([21,22]\). Clearly, induction of ovulation would jeopardise contraceptive protection and so the manufacturers of UPA advise that following use of UPA, additional barrier methods of contraception should be used until the next menstrual period \([101]\). However, based upon its half-life, UPA should, in theory, be virtually eliminated by 7 days. The Clinical Effectiveness Unit of the Faculty of Sexual and Reproductive Healthcare, UK, have recently published guidance recommending that in the absence of evidence, it would seem reasonable to advise women who are initiating hormonal contraception immediately after UPA, to either abstain or to use barrier methods for 14 days (based upon an expert opinion of 7 days to eliminate UPA plus a further 7 days for ovarian quiescence on hormonal contraception = 14 days) \([102]\).

Concomitant administration of UPA and medicinal products that increase gastric pH (e.g., proton-pump inhibitors, antacids and H\(_2\) receptor antagonists) is not
recommended since these may reduce plasma concentrations of UPA with a possible decrease in efficacy of UPA [101]. However, food interaction studies show that UPA can be taken with or without food.

**Pregnancy & breast-feeding**
So far, only a very small number of pregnancies have been exposed to UPA. In an agreement between the EMA and the market authorization holder, HRA Pharma, a registry has been created to collect robust data on any pregnancy exposed to UPA, such as an unrecognized pregnancy before EC intake or following treatment failure, in order to collect robust data regarding pregnancy outcomes in women exposed to UPA.

To date, it is unknown whether UPA is excreted in human milk, as such, studies have not yet been conducted. However, since UPA is a lipophilic compound, it may theoretically be excreted in human milk. Therefore, until more data become available, breastfeeding women who require EC and who take UPA are advised not to breastfeed for 36 h following UPA intake [9]. For LNG, the corresponding recommendation is to avoid breastfeeding for at least 8 h, but not more than 24 h after LNG intake [23].

**Future perspective**
Given the finding that pregnancy after EC is more likely amongst women who go on to have other episodes of sex in the same cycle as EC has been given, there is increasing realization of the need for women to start effective methods of contraception immediately after EC [24]. This concept is often referred to as ‘quick start’ or ‘bridging’ [25]. Given the concern that potential interactions between UPA and hormonal contraception could in theory reduce the efficacy of ongoing contraception, the manufacturer advises abstinence/condoms for the remainder of the menstrual cycle in which UPA is used [101]. Clearly, however, this guidance is not evidence-based and clinical research studies in this area are required so that we can best advise women on the need for additional contraceptive measures.

Another important area for future research, where data currently do not exist, is repeat use of UPA in the same cycle. Studies have already been conducted of repeated post-coital use of LNG and whilst this approach to contraception is not optimal, a Cochrane review concluded that, although it may be associated with menstrual irregularities, its efficacy may be better than no method of contraception [26]. Pilot studies of weekly administration of the SPRM mifepristone have also been conducted and this regimen has been shown to cause disruption to ovulation and irregular menstrual bleeding [27–30].

Research efforts should also be focused on developing a vaginal product containing UPA with a microbicide that offers ‘dual protection’ against sexually transmitted infections in addition to EC. This concept has already been explored in pilot studies with vaginal administration of LNG [31–33].

Future research is also required to explore noncontraceptive health benefits of UPA, such as possible beneficial effects on breast tissue. An antiproliferative effect of the SPRM mifepristone in breast tissue has been observed when given to women of fertile age [34]. Any possible protective effect of SPRMs, such as UPA against breast cancer, would be a highly desirable advantage of a contraceptive method and should be further investigated. Other areas where UPA, like other SPRMs, might be expected to have potential application are for gynecological indications such as fibroids or endometriosis [35–37].

**Conclusion**
Ulipristal acetate is a second-generation SPRM specifically developed for EC and is licensed for use up to 5 days after unprotected intercourse. This extended
time limit is an important advance since women who previously would not have presented for EC thinking that they were too late (after 72 h) for an orally active method, might now avail themselves of this method.

Ulipristal acetate has also been demonstrated to be more efficacious than LNG, but just as well tolerated. UPA will therefore be welcomed by both women and providers of contraceptive services as a real advance in EC technology.

Recommendations
Although the main mechanism of action of both LNG and UPA for EC is preventing ovulation, the ‘window of effect’ for LNG seems to be rather narrow, beginning after selection of the dominant follicle, and ending when LH begins to rise. By contrast, UPA has been demonstrated to have a direct inhibitory effect on follicular rupture. This allows UPA to be effective even when administered shortly before ovulation when the LH surge has already started to rise, a time period when use of LNG is no longer effective.

Thus, to help women prevent an unwanted pregnancy after unprotected intercourse at any time during the menstrual cycle, a single dose of 30 mg UPA should be recommended for use as soon as possible, and no later than 120 h (5 days) after intercourse. Further acts of unprotected intercourse after EC use should be avoided to prevent the risk of pregnancy at the time of the delayed ovulation. Effective contraception should be resumed/started as soon as possible after EC use and barrier contraception should be used for the initial 14 days.

Financial & competing interests disclosure
K Gemzell-Danielsson serves as a board member of an Advisory board of HRA-Pharma and ST Cameron was PI for a clinical study comparing efficacy of ulipristal acetate and levonorgestrel for emergency contraception and has received lecture honoraria from HRA Pharma. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

Executive summary
- A single dose of ulipristal acetate (UPA) 30 mg has recently been approved for emergency contraception (EC) use up to 120 h following unprotected intercourse. Meta-analysis has shown UPA to be more effective than levonorgestrel (LNG) but with similar side effects.
- Cost–effectiveness analysis has calculated that the cost of preventing one unintended pregnancy with UPA is significantly cheaper than the costs of induced abortion or childbirth.
- The main mechanism of action of both LNG and UPA for EC is delaying or inhibiting ovulation.
- UPA appears to have a direct inhibitory effect on follicular rupture, which makes it effective even when administered shortly before ovulation, a time period when use of LNG is no longer effective.
- Further studies are needed on the repeat use of UPA, as well as on its possible interaction with regular hormonal contraception.
- Future research is necessary to explore the potential noncontraceptive health benefits of UPA.
- UPA, a new type of second-generation progesterone-receptor modulator, represents an evolutionary step in EC treatment.

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Demonstrates that early luteal phase administration of a dose of UPA equivalent to that used for emergency contraception (EC) did not retard histological development of the endometrium.

Reports the findings of the first randomized controlled trial (RCT) to compare the efficacy of UPA and LNG.

Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised controlled trial (RCT) to compare the efficacy of UPA and LNG.


This noncomparative study of late intake after unprotected sex demonstrates that efficacy of UPA does not diminish with increasing time from sex to EC intake (between 48 and 120 h).


This cost–effectiveness study used the efficacy data from the meta-analysis of Glasier et al. 2010 and calculated that the cost of preventing one additional pregnancy by using UPA (GBP311) rather than LNG was significantly cheaper than induced abortion (GBP672) or childbirth (GBP2380).


Ulipristal acetate (UPA) is demonstrated to be a more potent inhibitor of ovulation than levonorgestrel (LNG), particularly at mid-cycle when risk of pregnancy is greatest.

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