

# EllaOne<sup>®</sup>: a second-generation emergency contraceptive?

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## Introduction

Autumn 2009 has seen the launch of EllaOne<sup>®</sup>, a new, single-dose, oral preparation to help prevent pregnancy after unprotected sexual intercourse (UPSI) or when contraception fails.<sup>1</sup> Is this a real advance, given that EllaOne is three times as expensive as levonorgestrel (LNG) 1500 µg (Levonelle<sup>®</sup>)?

## What is EllaOne?

EllaOne contains 30 mg ulipristal acetate (UPA), a synthetic selective progesterone receptor modulator, which has antagonistic and partial agonistic effects at the progesterone receptor level. Consequently, UPA should prevent the gene transcription normally activated by progesterone to produce the necessary proteins to support pregnancy. Over the last 10 years, other progesterone receptor modulators have been studied and shown to be effective postcoital contraceptives;<sup>2,3</sup> however, interest grew in using UPA as, in contrast to those previously studied, it has little anti-glucocorticoid activity.<sup>4</sup>

## What is new about EllaOne?

EllaOne is licensed for use as an emergency contraceptive if the first episode of UPSI or contraceptive failure has occurred within the previous 5 days.<sup>1</sup> At the present time, the only oral emergency contraceptive available in the UK is LNG 1500 µg licensed for use up to 72 hours after UPSI. However, it is now standard practice to offer LNG 1500 µg to women who have had UPSI within the last 120 hours if they decline a copper intrauterine device (IUD).<sup>5</sup>

## What is its mode of action?

There are few published data on UPA (or CDB-2914); however, it is thought that EllaOne's primary mode of action is to inhibit or postpone ovulation, with a secondary effect of altering the endometrium and thus preventing implantation.<sup>1</sup>

## How effective is EllaOne?

One initial study investigating a slightly higher dose of UPA (50 mg) found that it was as effective as using LNG within 72 hours of UPSI.<sup>6</sup> A Phase III study recruited 1241 women who had requested emergency contraception from 48 to 120 hours after UPSI or contraceptive failure.<sup>7</sup> Unlike LNG 1500 µg,<sup>8</sup> UPA 30 mg demonstrated sustained efficacy over time with an overall pregnancy rate of 2.1% and pregnancy rates of 2.3%, 2.0% and 1.3%, respectively, for time intervals of 48–72, 73–96 and 97–120 hours.<sup>7</sup>

Furthermore, in a head-to-head randomised controlled study where women, who presented up to 120 hours after UPSI or contraceptive failure, were given either a single dose of 30 mg UPA or 1500 µg LNG, pregnancy rates were

1.6% (95% CI: 0.9–2.7) for UPA and 2.6% (95% CI: 1.7–3.9 for LNG, with an odds ratio for UPA vs LNG of 0.59 (95% CI: 0.31–1.14). Although this result is not statistically significant, when the number of pregnancies prevented was calculated, UPA prevented more pregnancies than LNG ( $p < 0.05$  for a one-sided test).<sup>9</sup>

## Are there any side effects with UPA?

Although UPA has a high affinity for the glucocorticoid receptor, no adverse effects have been seen in humans. It has no affinity for human estrogen or mineralocorticoid receptors and only a minimal affinity to androgen receptors.<sup>1</sup>

In clinical studies (as yet unpublished) nearly 3400 women have taken UPA and adverse reactions are reported to be mild or moderate, resolving spontaneously. There were no serious adverse reactions in these studies.<sup>1</sup>

Very common side effects appear to be abdominal pain and menstrual changes. Other common side effects occurring in between 1:10 and 1:100 women included headache, nausea, vomiting, mood disorders and menstrual disturbance.<sup>1</sup>

## What about menstrual changes?

Most women (80.8%) will menstruate at their expected time or within 7 days of the expected time. Menstruation will occur earlier (>7 days) in about 6% and later ( $\geq 7$  days) in 19.2% of women. For a small number of women (5.1%) the delay will be greater than 20 days, with 0.5% experiencing a delay of more than 60 days. In research studies almost 80% (79%) of women said that their menstrual volume was normal, 16% said it was heavy and 5% described it as 'spotting'.<sup>1</sup>

This change in menstruation may cause concern to some women who may think they are pregnant. Clear guidance about menstrual changes will need to be given by the prescribing health care professional to ensure women are not unduly worried and pregnancy tests offered where necessary.

## Who can take EllaOne?

Most women can take this product (except if they have severe hepatic impairment or poorly controlled asthma) and they should take it as soon as possible after UPSI.<sup>1</sup> If a woman vomits within 3 hours of taking this preparation then another tablet should be taken.<sup>1</sup> EllaOne is not recommended for repeated administration during the same menstrual cycle as there are no supportive safety or efficacy data.<sup>1</sup>

## Are there any drug interactions with EllaOne?

It is known that UPA is metabolised by CYP3A4 *in vitro*, therefore CYP3A4 inducers such as the rifamycins, phenytoin, phenobarbital, carbamazepine and St John's Wort may reduce the concentration of UPA. It is uncertain whether this will affect the efficacy of the product and no advice has been given about changing the dose of UPA.<sup>1</sup>

Plasma concentrations of UPA may also be affected by medicinal products that increase gastric pH such as proton pump inhibitors and antacids, and therefore their concomitant use is not recommended.<sup>1</sup>

Potent CYP3A4 inhibitors such as ketoconazole and itraconazole may increase plasma concentrations of UPA; the clinical significance of this is unknown.<sup>1</sup>

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One important potential interaction may affect the prescribing of hormonal contraception immediately after EllaOne is administered. As described earlier, UPA binds to the progesterone receptor and may theoretically interfere and decrease the action of combined hormonal and progestogen-only contraceptives. This will potentially affect women requiring emergency contraception because of missed pills: with LNG 1500 µg women are advised to immediately continue with their pill packet; however, if EllaOne is used, women are advised to additionally use 'reliable' barrier contraception until their next period.<sup>1</sup> No advice is provided for women taking progestogen-only pills who may be amenorrhoeic. As we are now focusing on providing an effective 'contraceptive bridge' following administration of emergency contraception to decrease unplanned pregnancy, I think this is a serious flaw with progesterone receptor modulators. Those undertaking research in this field need to urgently address this issue.

### Will EllaOne adversely affect a pregnancy?

No reassurance can be given to women who become pregnant after taking EllaOne as there are only limited data suggesting no teratogenic potential. Following the product launch, however, HRA Pharma are maintaining a pregnancy registry to record the outcomes of pregnancies occurring in women taking EllaOne.<sup>1</sup>

### What about women who are breastfeeding?

EllaOne is lipophilic and theoretically may be excreted in breast milk. As its effects are unknown it is advised that breastfeeding should be avoided for at least 36 hours after taking EllaOne.<sup>1</sup>

### Will EllaOne have a 'black triangle' and can it be included in PGDs?

EllaOne will be a 'black triangle' drug. 'Black triangle' products are newly launched drugs or vaccines for which relatively limited information about their safety is available from clinical trials. These drugs are intensely monitored by the Commission on Human Medicines and the Medicines and Healthcare products Regulatory Agency in order to confirm their risk/benefit profile. Consequently, health care professionals should report all suspected drug reactions; and the 'black triangle' status will only be removed once product safety has been established.<sup>10</sup>

Many health care professionals issue oral emergency contraception under patient group directions (PGDs), so can a 'black triangle' drug be included in such a directive? Legally, 'black triangle' drugs can be included but the practice is discouraged. They are normally only included in PGDs if there is a clear case for administration/supply.

### What will be the place for EllaOne?

Progesterone receptor modulators appear to be more effective than LNG, especially when taken between 72 and 120 hours after UPSI, and their efficacy does not decrease over time.<sup>3,7,9</sup> Although EllaOne appears expensive, an argument could be made to use this in preference to LNG 1500 µg for women presenting between 3 and 5 days after UPSI, particularly when the cost of an unplanned pregnancy is taken into account. I look forward to seeing more in-depth comparative work investigating this product versus LNG 1500 µg.

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### References

- 1 Ellaone®. Summary of Product Characteristics. June 2009. <http://www.emea.europa.eu/humandocs/PDFs/EPAR/ellaone/H-1027-PI-en.pdf> [Accessed 4 August 2009].
- 2 von Hertzen H, Piaggio G, Ding J, Chen J, Song S, Bártfai G, *et al*; WHO Research Group on Post-ovulatory Methods of Fertility Regulation. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. *Lancet* 2002; **360**: 1803–1810.
- 3 Cheng L, Gülmezoglu AM, Piaggio G, Ezcurra E, Van Look PF. Interventions for emergency contraception. *Cochrane Database Syst Rev* 2008; **2**: CD001324.
- 4 Attardi BJ, Burgenson J, Hild SA, Reel JR, Blye RP. CDB-4124 and its putative monodemethylated metabolite, CDB-4453, are potent antiprogesterins with reduced antiglucocorticoid activity: *in vitro* comparison to mifepristone and CDB-2914. *Mol Cell Endocrinol* 2002; **188**: 111–123.
- 5 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance (April 2006). Emergency contraception. *J Fam Plann Reprod Health Care* 2006; **32**: 121–128. [http://www.ffprhc.org.uk/admin/uploads/449\\_EmergencyContraceptionCEUGuidance.pdf](http://www.ffprhc.org.uk/admin/uploads/449_EmergencyContraceptionCEUGuidance.pdf) [Accessed 4 August 2009].
- 6 Creinin MD, Schlaff W, Archer DF, Wan L, Frezieres R, Thomas M, *et al*. Progesterone receptor modulator for emergency contraception: a randomized controlled trial. *Obstet Gynecol* 2006; **108**: 1089–1097.
- 7 Fine P, Ginde S, Morfesis J, Mathé H, Gainer E. A multicenter trial of ulipristal acetate for late-intake emergency contraception. Abstract presented at the 8th Congress of the European Society of Gynecology, Rome, Italy, 10–13 September 2009.
- 8 Piaggio G, von Hertzen H, Grimes DA, Van Look PF. Timing of emergency contraception with levonorgestrel or the Yuzpe regimen. Task Force on Postovulatory Methods of Fertility Regulation. *Lancet* 1999; **353**: 721.
- 9 Cameron S, Glasier A, Fine P, Mathé H, Gainer E. Ulipristal acetate compared to levonorgestrel for emergency contraception within five days of unprotected intercourse: a randomized controlled trial. Abstract presented at the 8th Congress of the European Society of Gynecology, Rome, Italy, 10–13 September 2009.
- 10 Medicines and Healthcare products Regulatory Agency. Black Triangle Scheme. <http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Medicines/Reportingsuspectedadversedrugreactions/Healthcareprofessionalreporting/BlackTriangleScheme/index.htm> [Accessed 4 August 2009].

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