

Ulipristal acetate: An update for Australian GPs

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Background

In Australia, use and understanding of emergency contraception among women remains relatively low. This is despite the introduction of levonorgestrel emergency contraceptive pills (ECPs) more than a decade ago. In April 2016, a new ECP with the active ingredient ulipristal acetate became available in Australia.

Objectives

The aims of this article are to increase understanding of the recently introduced ulipristal acetate ECP, including its safety profile, efficacy and special considerations; dispel common myths and misconceptions about emergency contraception; and to provide guidance on emergency contraceptive management in general practice, considering the recent advances.

Discussion

Women are more receptive to information about emergency contraception that has been provided by a general practitioner (GP). As such, the availability of the ulipristal acetate ECP in Australia provides an important opportunity for GPs to help women prevent unplanned pregnancies.

The first dedicated Australian emergency contraceptive pill (ECP), which contains levonorgestrel, was registered as a prescription item in 2002 and made available over the counter shortly thereafter. Since then, there has been an understandable decline in emergency contraception management in general practice.¹ Despite the availability of the ECP in Australia for more than a decade, use and understanding among Australian women remain relatively low.^{2–4} The availability of a new emergency contraceptive in Australia – ulipristal acetate – provides new opportunities in general practice to educate women about preventing unplanned pregnancies. The purpose of this paper is to highlight the availability of ulipristal acetate in Australia and to describe its role as an emergency contraceptive.

What is ulipristal acetate?

Ulipristal acetate is a selective progesterone receptor modulator.⁵ It is a partial agonist, exerting agonist and antagonist activity at the progesterone receptor. While it has been used in the medical management of uterine fibroids,⁶ it is more commonly used for emergency contraception. Ulipristal acetate is taken as a single 30 mg dose as soon as possible after unprotected intercourse, but has continuing efficacy up to five days later (120 hours), compared with 72 hours for levonorgestrel ECP.

Ulipristal acetate became available as an ECP in the European Union in 2009. This was followed by its release in the US in

2010. In March 2016, it became available in Australia as a Schedule 4 (prescription) item but, following approval by the Therapeutic Goods Administration (TGA),⁷ from 1 February 2017 it has become a Schedule 3 (pharmacist only) item, available over the counter (similar to the levonorgestrel). The retail cost of ulipristal acetate has been approximately \$50 on prescription but this may well come down as a Schedule 3 item.

How does ulipristal acetate work?

Depending on when ulipristal acetate is taken during the menstrual cycle, it will either prevent or delay ovulation.⁸ It does this more effectively than levonorgestrel.⁸ Ulipristal acetate delays ovulation by at least five days when given before the onset of the luteinising hormone (LH) surge in 100% of cycles; in comparison, levonorgestrel only achieves this in 25% of cycles.⁸ When administered once the LH surge has commenced, but before it peaks, ulipristal acetate delays ovulation in 79% of cycles, whereas levonorgestrel delays ovulation in only 14% of cycles.⁸ Once the LH surge has reached its peak, neither ulipristal acetate nor levonorgestrel has any effect on ovulation.⁸

Is ulipristal acetate better than levonorgestrel?

The evidence suggests that ulipristal acetate is a more effective form of emergency contraception than levonorgestrel (Table 1).⁹ Ulipristal acetate

is twice as likely as levonorgestrel to prevent pregnancy when used within 72 hours or within five days of unprotected intercourse.⁹ When taken within the first 24 hours after intercourse, it reduces unplanned pregnancies by two-thirds when compared with levonorgestrel.⁹

Any concerns about safety or tolerability?

The most commonly reported adverse effects following ulipristal acetate administration are headache, nausea, abdominal pain and dysmenorrhea,⁵ but these effects are typically mild or moderate and resolve spontaneously. The safety profile of ulipristal acetate is comparable to that of levonorgestrel,⁹ as outlined in the UK Medical Eligibility Criteria¹⁰ and reflected by the fact that the TGA has now scheduled it as an over-the-counter drug.

Special considerations Starting contraception after ulipristal acetate

In recent years general practitioners (GPs) have come to use the 'quick start' method of contraception (starting contraception straight away rather than waiting for the next period) following use of emergency contraception, to ensure that women are rapidly protected and do not have to wait to commence contraception. However, given that ulipristal acetate is a selective progesterone receptor modulator, there are concerns that:

- its effect in delaying ovulation might be reduced by quick-starting a progestogen-containing contraceptive
- the effectiveness of a progestogen-containing contraceptive method might be compromised by having taken ulipristal acetate because of competition at the progesterone receptor site.¹⁰

The UK Faculty of Sexual and Reproductive Healthcare, therefore, recommends that after using ulipristal acetate for emergency contraception, a woman should not start a hormonal contraceptive method for at least five days and that she should use barrier methods or abstain from sex until effective hormonal contraceptive cover has been

achieved.¹⁰ This, in effect, means waiting for varying amounts of time, depending on which hormonal method of contraception is commenced (Table 2). Patients should also be advised to undertake a pregnancy test three weeks after commencement of the hormonal contraception.

The recommendation in the Approved Product Information is for a woman to use a barrier method until her next period,⁵ so as to minimise confusion.

If a woman presents requesting an ECP and her GP is able to insert an intrauterine device (IUD) or access rapid insertion (within five days) for the woman, then a copper IUD will provide both effective emergency contraception and ongoing long-acting reversible contraception. It is not appropriate to insert a hormonal IUD if a woman has received ulipristal acetate in that cycle. A bridging method should be offered until pregnancy can be excluded.¹⁰

Women who are overweight or obese

There remains continuing concern that oral forms of the ECP may be less effective in women with a higher body mass index (BMI).^{11–13} An exploratory analysis

of meta-analysis data found that women with a BMI ≥ 30 kg/m² become pregnant over three times more often in ECP clinical trials than those with a BMI in the normal range.¹³ This is a significant issue given the rising rates of overweight and obesity in women in Australia. The decline in efficacy occurs as BMI increases, but appears to be better for ulipristal acetate, which has a threshold of 88 kg, compared with 70 kg for levonorgestrel.¹³ Ideally, a copper IUD should be inserted for emergency contraception in women with a BMI >25 kg/m² as it has $>99\%$ efficacy and offers excellent ongoing long-term contraception. However, if this is not an option, ulipristal acetate should be recommended as first-line contraception.¹³ Doubling the dose of the levonorgestrel ECP may also be an option for women who are obese but the evidence for this strategy is pending.¹¹

Women who are breastfeeding

Emergency contraception is not required if unprotected sexual intercourse or barrier method failure occurs up to three weeks postpartum.¹⁴ From three weeks it may be required if lactational amenorrhoea cannot be relied on as a contraceptive (failure rate

Table 1. Percentage of pregnancies in meta-analysis according to time from unprotected sex to administration of emergency contraception⁹

Administration	Levonorgestrel	Ulipristal acetate	Odds ratio (95% CI)*
Within 24 hours	2.3%	0.9%	0.35 (0.11, 0.93)
Within 72 hours	2.2%	1.4%	0.58 (0.33, 0.99)
Within 120 hours	2.2%	1.3%	0.55 (0.32, 0.93)

Table 2. Hormonal contraception use after administration of ulipristal acetate¹¹

Ulipristal acetate = day 0	Method (day ulipristal acetate + 5)	Required duration of additional (barrier) contraception
Ulipristal acetate then wait at least five days	Combined oral contraceptive pill (except estradiol valerate/dienogest)	7 days
	Estradiol valerate/dienogest	9 days
	Combined vaginal ring	7 days
	Progestogen-only pill (traditional/desogestrel)	2 days
	Progestogen-only implant or injectable	7 days

of approximately 2%). It is recommended that women must be fully breastfeeding day and night, with no long intervals between feeds day or night (eg >4 hours during the day and >6 hours at night), amenorrhoeic, and less than six months' postpartum).¹⁵

Peak bodies have endorsed the use of the levonorgestrel ECP for women who are breastfeeding;¹⁴ however, ulipristal acetate is excreted in breast milk and the impact on infants has not been studied.⁵ As a precautionary measure, therefore, breastfeeding is not recommended for one week after ulipristal acetate intake.⁵ The copper IUD should also be considered as an effective and hormone-free option.

Conclusion

The availability of ulipristal acetate in Australia provides an opportunity for GPs to re-engage with the issue of emergency contraception. Women are more receptive to emergency contraception information when a GP provides it.¹ GPs can help women to have greater self-efficacy in preventing unplanned pregnancy by:

- informing women about the different emergency contraceptive options available (ulipristal acetate ECP, levonorgestrel ECP and the copper IUD)
- highlighting their relative benefits (the increased efficacy of ulipristal acetate as opposed to levonorgestrel); and
- noting the current scheduling (both levonorgestrel and ulipristal acetate are Schedule 3).

There are also opportunities during this kind of consultation to dispel any myths or misconceptions women may have (Box 1) and GPs can conduct other activities during the emergency contraception consultation, such as health promotion, checking for sexually transmissible infections, such as *Chlamydia trachomatis*, and referrals and management for ongoing contraception.¹ Ultimately, emergency contraception should only be for emergencies; focus is needed on informing women about, and helping them to access, the more effective forms of longer term contraception that might suit them.

Case 1

Elizabeth, 20 years of age, makes an urgent appointment with you. She is nulliparous and a full-time student. Her weight and BMI are in the healthy range. Elizabeth explains that the condom broke last night, resulting in her unintentionally having unprotected sex with her boyfriend. Elizabeth was on the oral contraceptive pill but forgot to renew her prescription two months ago and has since been using barrier methods. She knows that the instance of unprotected sex happened fourteen hours ago but is unsure when her last period was, citing approximately two weeks ago as a possibility. Elizabeth states that she 'really isn't ready for a baby'.

As Elizabeth does not want an IUD (99% effective for emergency contraception),

her options are the levonorgestrel ECP or ulipristal acetate ECP. She can take either as she does not take any CYP3A4 (liver enzyme) inducers.^{5,16} Table 3 summarises the advice to give Elizabeth.

Case 2

Marie, 35 years of age, sees her GP after having unprotected sex two days ago. Marie has three children. She does not wish to have any more children, is not in a relationship, and is not currently using ongoing contraception. Marie is 157 cm and weighs 80 kg. Her BMI is 32.5 kg/m², classifying her within the obese range. The efficacy of levonorgestrel decreases when administered to overweight and obese women.^{11–13} Aside from a copper IUD, ulipristal acetate is her best option

Box 1. Common myths and misconceptions concerning emergency contraception

As a trusted source of information about the emergency contraception pill (ECP), general practitioners have an important role to play in dispelling myths and misconceptions thereby increasing knowledge of how and when to use emergency contraception, and subsequent use of the ECP.

Myth: The timing of ovulation is easy to predict.

Reality: Ovulation is unpredictable and timing is more difficult to determine than is commonly thought.¹⁷ More than 50% of women ovulate outside of days 12–16 (mid-range).^{17,18}

Myth: Every instance of unprotected sex will lead to pregnancy.

Reality: Unprotected sex sometimes results in pregnancy. The likelihood of pregnancy occurring varies, depending on when unprotected sex happens relative to ovulation; fertilisation is most likely when unprotected sex happens near the time of ovulation.¹⁹

Myth: Hormonal emergency contraception causes abortion.

Reality: No abortifacient effects among women have been reported following administration of ECPs at any dose.^{20,21}

Myth: Emergency contraception is only for the 'morning after' unprotected sex.

Reality: Some forms of emergency contraception are indicated for use up to five days after unprotected sex. ECPs should be administered as soon as possible after unprotected sex.

Myth: Increasing access to emergency contraception increases sexual and/or contraceptive risk-taking.

Reality: Studies show that women with greater access to emergency contraception are not more likely to engage in unprotected intercourse and, conversely, are more likely to adopt an ongoing contraceptive method after using emergency contraception.^{22,23}

Myth: Taking ECPs will affect future fertility.

Reality: Use of ECPs has no impact on future fertility.^{5,20}

Myth: Hormonal emergency contraception provides ongoing protection against subsequent acts of unprotected sex.

Reality: Hormonal emergency contraception does not provide ongoing protection against subsequent acts of unprotected sex.^{5,16} The copper intrauterine device is the only form of emergency contraception that provides ongoing contraceptive protection.

Myth: Emergency contraception prevents pregnancy in every case.

Reality: No contraception is 100% effective. Emergency contraception does not prevent pregnancy in every case.

Table 3. Advice for Elizabeth regarding ulipristal acetate and levonorgestrel ECPs^{5,24}

Topic	Ulipristal acetate	Levonorgestrel
Administration	Take as soon as possible. Take orally with or without food. Do not take levonorgestrel also. If vomiting occurs within three hours, take another.	Take as soon as possible. Take orally with or without food. Do not also take ulipristal acetate. If vomiting occurs within two hours, take another.
Risk of pregnancy/ efficacy	No emergency contraception is 100% effective. If taken within 24 hours, pregnancy risk is 0.9% ¹⁰	No emergency contraception is 100% effective. If taken within 24 hours, pregnancy risk is 2.3%. ¹⁰
Next period	Can occur a few days earlier or later than expected. Take a pregnancy test if period is more than seven days late.	Can occur a few days earlier or later than expected. Take a pregnancy test if period is more than seven days late.
Ongoing contraception	If wanting to restart on combined oral contraception do not start for five days. Then start on an active hormone tablet no matter if spotting or not Make an appointment for five days time for contraceptive implant insertion?	Recommence the pill today/? Contraceptive implant insertion today?
STI check	An opportunistic STI test should be undertaken ²⁴	An opportunistic STI test should be undertaken ²⁴

STI, sexually transmissible infection

for avoiding unintended pregnancy and she should take it as soon as possible. It would be important to talk to Marie about long-acting reversible contraception.

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Competing interests: None.

Provenance and peer review: Not commissioned, externally peer reviewed

Acknowledgements

I would like to thank Heather Morecroft from MS Health for her assistance in the preparation for the manuscript.

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