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Ulipristal Acetate
A Review of Its Use in Emergency Contraception

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Data Selection

Sources: Medical literature (including published and unpublished data) on 'ulipristal' was identified by searching databases since 1996 (including MEDLINE and EMBASE and in-house AdisBase), bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search terms were 'ulipristal' or 'ulipristal acetate', and 'emergency contraception'. Searches were last updated 21 April 2011.

Selection: Studies in females requesting emergency contraception who received ulipristal acetate. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Ulipristal acetate, emergency contraception, pharmacodynamics, pharmacokinetics, progesterone receptor modulator, therapeutic use.

Contents

Abstract

Ulipristal acetate (ellaOne®; ella®) is the first of a new class of selective progesterone receptor modulators, and is indicated for emergency contraception within 120 hours after unprotected sexual intercourse or contraceptive failure. The principal effect of ulipristal acetate is to inhibit or delay ovulation. This effect

may result from the drug's ability to delay the onset of luteinizing hormone (LH) surge or postpone LH peak if LH surge has started, or possibly by a direct inhibitory effect on follicular rupture, when administered in the follicular phase (including just before ovulation).

In clinical trials, a single oral dose of ulipristal acetate 30 mg was effective in preventing pregnancies in women requesting emergency contraception after unprotected sexual intercourse and provided sustained efficacy throughout the 120-hour postcoital period in which it is indicated. When compared with levonorgestrel in well designed noninferiority trials, it was no less effective in preventing pregnancies when administered within 72 hours of unprotected intercourse, but was more effective when administered later (within 72–120 hours). Results of a meta-analysis suggest that ulipristal acetate may be more effective than levonorgestrel from day 1 and throughout the entire 5-day period following unprotected sexual intercourse.

Ulipristal acetate is generally well tolerated, with a similar tolerability profile to that of levonorgestrel. In general, the onset of menses is delayed by 2–3 days following treatment. Although, ulipristal acetate is more expensive than levonorgestrel, it may represent a cost-effective alternative to levonorgestrel for women requesting emergency contraception within 120 hours of unprotected intercourse. Thus, ulipristal acetate provides effective, sustained and well tolerated emergency contraception when taken within 120 hours of unprotected sexual intercourse, thereby offering an extended treatment window compared with levonorgestrel, which should be administered within 72 hours.

1. Introduction

Despite the widespread availability of highly effective methods of contraception, many unplanned pregnancies occur. In both the US[1] and EU[2] it is estimated that about half of all pregnancies are unplanned and, in the US, this equates to more than 3 million pregnancies each year.[1]

Unplanned pregnancies have been linked to a range of health, social and economic consequences, including negative perinatal outcomes, negative effects on parental relationship stability and financial insecurity.[1] While the impact of emergency contraception on relieving these and other negative outcomes is less well defined than that of contraception *per se*, it is recognized that postcoital emergency contraception, which is largely underutilized worldwide, could result in the avoidance of millions of unplanned pregnancies each year.[3,4]

Emergency contraception is defined as the use of a drug or device to prevent an unwanted pregnancy after unprotected sexual intercourse.[5] It offers women a second chance to prevent an unplanned pregnancy when regular contraception fails, no method was used or sex was forced. Currently available methods include oral hormones (e.g. ulipristal acetate, levonorgestrel) or a copper-bearing intra-uterine device.

The first oral hormonal regimen designed specifically for emergency contraception consisted of a combination of oestrogen and progesterone (commonly known as the Yuzpe regimen).[6] Subsequently, the progestin levonorgestrel and the progesterone receptor antagonist mifepristone gained popularity, as they were associated with fewer adverse effects and greater efficacy than the Yuzpe regimen.[4,7] While low-dose mifeprestone (10–50 mg) is an effective and well tolerated emergency contraceptive, its use in this indication has been limited for social and political reasons.[4] To date, mifepristone is only available for emergency contraception in Russia and China.[6]

Levonorgestrel is currently the most commonly used hormonal method for emergency contraception. However, while its efficacy is well established, in clinical trials pregnancy was not prevented in 20–30% of women who received the drug.[8,9]

Furthermore, although levonorgestrel (single-dose 1.5 mg tablet) is approved for use within 72 hours of unprotected intercourse, it is most efficacious when taken as early as possible.[10]

Ulipristal acetate (ellaOne®; ella®; formerly known as CDB-2914) is the first of a new class of selective progesterone receptor modulators (figure 1).[11] It was developed specifically for emergency contraception and is approved for use up to 120 hours after unprotected intercourse.[12,13] This article summarizes the pharmacological properties of the drug and reviews clinical trials, including those that compared its use with that of levonorgestrel, in women requiring emergency contraception following unprotected sexual intercourse.

2. Pharmacodynamic Properties

Ulipristal acetate is an orally active, synthetic, selective progesterone modulator that acts by binding with high affinity to the human progesterone receptor,[13] where it has both antagonist and partial agonist effects.[6] The drug has minimal affinity for the androgen receptor and no affinity for the human oestrogen or mineralocorticoid receptors.[13] Although ulipristal acetate has some affinity for the glucocorticoid receptor in animals, no antiglucocorticoid effects have been observed in humans. Moreover, its glucocorticoid receptor antagonist activity is much reduced compared with that of mifepristone,[14] indicating that ulipristal acetate belongs to a new class of progesterone receptor modulators with dissociated antiglucocorticoid activity.

The principal effect of ulipristal acetate is to inhibit or delay ovulation, but the mechanism by which this occurs has not been fully clarified.[13,15] It may act by inhibiting or delaying the luteinizing hormone (LH) surge, postponing LH peak if LH surge has already commenced, or possibly by directly inhibiting follicular rupture.[15,16]

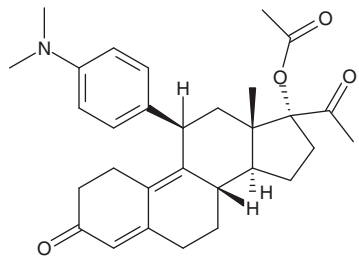

Fig. 1. Chemical structure of ulipristal acetate.

In a placebo-controlled study in women with normal menstrual cycles, single doses of ulipristal acetate 10, 50 or 100 mg administered at the mid-follicular stage (lead follicle diameter of 14–16 mm) significantly suppressed lead follicle growth ($p = 0.001$), which led to a dose-dependent delay in folliculogenesis ($p < 0.0001$) and suppression of plasma estradiol levels ($p < 0.001$).[17] A subsequent randomized, double-blind, crossover study showed that a single dose of ulipristal acetate 30 mg given immediately before ovulation significantly ($p < 0.0001$) delayed follicular rupture compared with placebo.[15] As this group included women in whom the onset of the LH surge had already commenced, these results indicate that ulipristal acetate is effective in postponing the LH peak and delaying follicular rupture during a longer fertile window than levonorgestrel, which needs to be administered before the onset of LH surge in order to effectively prevent pregnancy.[18] However, if ulipristal acetate was administered after the LH peak was reached, follicular rupture was not delayed.[15] Results of animal studies suggest that ulipristal acetate may have a direct inhibitory effect on follicular rupture.[16]

Endometrial thickness was reduced in a dose-dependent manner following a single dose of ulipristal acetate 10, 50 or 100 mg ($p \leq 0.007$ for all doses combined vs placebo) given in the early luteal phase and within 2 days of LH surge.[19] However, the decrease appeared to be minimal with the 10 and 50 mg doses. Furthermore, alterations in progesterone-dependent markers of implantation were also observed in endometrial glandular epithelium.[19]

When administered in the mid-luteal phase, ulipristal acetate had a dose-dependent effect on menses, with higher doses (100–200 mg) associated with early menses.[20] In clinical trials, cycle length was increased by a mean of approximately 2.5 days (section 5). There was no indication that cycle length was influenced by the time of the menstrual cycle in which the drug was given.[21]

3. Pharmacokinetic Properties

Pharmacokinetic data on ulipristal acetate are derived from studies in women, which are reported in the manufacturer's prescribing information.[12,13]

3.1 General Properties

Ulipristal acetate is rapidly absorbed. Mean peak plasma concentrations (C_{max}) of the drug (176 ng/mL) and the active major metabolite, mono-demethylated-ulipristal acetate (69 ng/mL), were reached (t_{max}) at 0.9 and 1.0 hours, respectively, in a study of 20 women under fasting conditions following administration of a single oral 30 mg dose.[12,13] Corresponding values for the area under the plasma concentration-time curve from time zero to infinity (AUC_∞) were 556 and 246 ng • h/mL.

When ulipristal acetate was taken together with a high-fat meal, mean C_{max} was reduced by ≈45%, t_{max} was delayed from a median of 0.75 hours to 3 hours, and mean AUC_∞ was increased by 25% compared with administration in the fasting state.[12,13] Similar results were observed with mono-demethylated-ulipristal acetate. However, the effect of concomitant food intake did not change the efficacy of ulipristal acetate in phase III trials.[22]

Ulipristal acetate is highly bound to plasma proteins (>94%), including albumin, alpha-1-acid-glycoprotein and high-density lipoprotein.[12,13] After ingestion, the drug is extensively metabolized in the liver to mono-demethylated, di-demethylated and hydroxylated metabolites, of which only the mono-demethylated metabolite is pharmacologically active. *In vitro* studies show that metabolism is predominantly mediated by cytochrome P450 (CYP) 3A4 enzymes, and to a lesser extent by CYP1A2 and CYP2D6.[12,13]

Ulipristal acetate is primarily excreted via the faeces. After a single dose of ulipristal acetate 30 mg, the terminal elimination plasma half-life is estimated at 32 hours for ulipristal acetate and 27 hours for mono-demethylated-ulipristal acetate.[12,13]

Pharmacokinetic studies in women with renal or hepatic impairment, or in women aged <16 years, have not been performed.[12,13] No differences in pharmacokinetic parameters were observed between women of different ethnic groups in clinical studies.[12] The drug's effect on the human embryo is unknown. Although repeated ulipristal acetate doses in animal studies resulted in some embryo-fetal loss, at doses low enough to maintain gestation, there was no indication of any teratogenic potential in these studies.[12,13]

3.2 Drug Interactions

Drug interaction studies with ulipristal acetate in humans have not been performed. However, as the drug is primarily metabolized by CYP3A4, drug interactions are possible when co-administered with agents that induce or inhibit CYP3A4.[12,13] Co-administration with CYP3A4 inducers (e.g. rifampicin, phenytoin) or agents that increase gastric pH (e.g. proton pump inhibitors, antacids) is not recommended as plasma concentrations of ulipristal acetate may be reduced, leading to a loss of efficacy. Co-administration with potent CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, ritonavir) may increase exposure to ulipristal acetate.[12,13] It is unknown whether this potential increase in exposure could be of clinical relevance.

As a result of its affinity for the progesterone receptor, ulipristal acetate may interfere with the action of progesterone. For example, it is possible that the contraceptive action of combined hormonal contraceptives and progesterone-only contraceptives may be reduced. It is recommended that ulipristal acetate is not co-administered with other emergency contraception containing levonorgestrel.

4. Clinical Efficacy

The efficacy of oral ulipristal acetate has been evaluated in a phase II[21] and two phase III[23,24] multicentre clinical trials in women requesting emergency contraception following unprotected sexual intercourse (table I). Two were randomized, single-[23] or double-blind,[21] noninferiority trials that primarily compared pregnancy rates between ulipristal acetate and levonorgestrel, and a third open-label study in the US compared

Table I. Efficacy of oral ulipristal acetate (UPA) in women requiring emergency contraception following unprotected sexual intercourse (UPSI). Results of primary analyses in one phase II[21] and two phase III[23,24] trials using the efficacy evaluable[21,23][a] or modified intent-to-treat[24][b] populations

Study	Study design	Study drug (mg)	No. of evaluable pts	Period after UPSI in primary analysis (h)	Outcome		
					pregnancy rate (%)	95% CI	OR UPA vs LNG (95% CI)
Creinin et al.[13,21]	r, db, mc, ni	UPA 50[c] + PL at 12 h	775	Within 72	0.9[d]	0.2, 1.6	0.50 (0.18, 1.24)
		LNG 0.75 + LNG 0.75 at 12 h	774		1.7	0.8, 2.6	
Fine et al.[24]	mc, ol	UPA 30	1241	48–120	2.1	1.4, 3.1[e]	
		EE[f]			5.5		
Glasier et al.[23]	r, sb, mc, ni	UPA 30	844	Within 72	1.8	1.0, 3.0	0.68 (0.35, 1.31)[g]
		LNG 1.5	852		2.6	1.7, 3.9	

a Efficacy evaluable populations included women aged ≤35 years who were not pregnant at baseline and whose pregnancy status after treatment was known.

b The modified intent-to-treat population excluded women aged >35 years, lost to follow-up, with unknown pregnancy status at follow-up or whose pregnancy was not compatible with emergency contraception failure.[24]

c Subsequent to this study, micronization of UPA allowed reduction of the dose from 50 to 30 mg when used in tablet form.

d As the predefined upper limit of 97.5% CI (0.77%) for the difference between treatments did not exceed 2%, the noninferiority of UPA vs LNG was demonstrated.

e As the predefined upper limit of the 95% CI of the observed rate was lower than the EE rate, the observed rate with UPA was considered to be significantly lower than the EE rate.

f Expected pregnancy rate (using methodology of Trussell et al.[25]) in the absence of emergency contraception.

g As the predefined upper limit of the 95% CI for the OR of pregnancy occurring with UPA vs LNG did not exceed 1.6, the noninferiority of UPA vs LNG was demonstrated.

db = double-blind; **EE** = estimated expected; **LNG** = levonorgestrel; **mc** = multicentre; **ni** = noninferiority; **ol** = open-label; **OR** = odds ratio; **PL** = placebo; **r** = randomized; **sb** = single-blind.

pregnancy rates between ulipristal acetate and those expected in the absence of emergency contraception.[24]

Women with regular menstrual cycles aged 16 (in the UK[23]) or 18 years or older seeking emergency contraception within 72[21] or 120[23,24] hours of unprotected sexual intercourse were eligible for enrolment. Women taking hormonal contraceptives or fitted with an intrauterine device were excluded. Ulipristal acetate was administered as a single dose of 30 mg, except in the phase II study in which ulipristal acetate 50 mg capsules were administered;[21] subsequent to this study micronization of the formula allowed a dose reduction from 50 to 30 mg when used in tablet form. In the active comparator studies, levonorgestrel was administered as a single 1.5 mg dose or two doses of 0.75 mg 12 hours apart (table I).

The primary efficacy endpoint in each study was the observed pregnancy rate in those who received treatment within 72 hours,[21,23] or between 48 and 120 hours of unprotected intercourse.[24] Across all trials, the mean age of women was 24–25 years, 60–70% were Caucasian, and about half had not been pregnant previously.[21,23,24] Reasons for requesting emergency contraception included a failed condom or no contraceptive methods used. The final efficacy evaluable[21,23] and modified intent-to-treat[24] populations (defined in table I) excluded those aged >35 years, as recommended by the US FDA because of reduced fertility in this group.

Results from noninferiority trials demonstrated that ulipristal acetate 30 mg was no less effective than levonorgestrel 1.5 mg when taken within 72 hours of unprotected sexual intercourse with regard to the pregnancy rate in efficacy evaluable populations (table I).[21,23] Similar results were observed in the intent-to-treat[23] and modified intent-to-treat (excluded women for whom a pregnancy outcome could not be evaluated)[21] populations.

In the open-label study,[24] the pregnancy rate in patients receiving ulipristal acetate within 48–120 hours of unprotected sexual intercourse was significantly lower than that of the expected pregnancy rate in the absence of emergency contraception (table I). Overall, ulipristal acetate reduced the pregnancy rate by 62.3%. In addition, as the upper limit of the 95% CI of the observed rate in patients receiving ulipristal acetate was lower than the clinical irrelevance threshold of 4%, the protocol definition of study success was met. The clinical irrelevance threshold was determined by halving the estimated expected pregnancy rate of 8% (as determined from results of previous studies) in the absence of contraception.

Also in this study, ulipristal acetate demonstrated sustained efficacy when administered at any time throughout the 48- to 120-hour period after unprotected intercourse.[24] Observed pregnancy rates for 2–3, 3–4 and 4–5 days were 2.3%, 2.1% and 1.3%, respectively.

Pregnancy rates with ulipristal acetate (1.8% vs 5.5%) and levonorgestrel (2.6% vs 5.4%) were both significantly ($p = 0.001$ for both) lower than expected rates in the phase III noninferiority study.[23] In this same study, although the pregnancy rate was not significantly different between ulipristal acetate or levonorgestrel treatment groups when either agent was taken within 120 hours of unprotected intercourse (odds ratio 0.57; 95% CI 0.29, 1.09), a treatment difference became evident for the latest period.[23] When either agent was taken within 72–120 hours of unprotected intercourse, there were significantly fewer pregnancies (0 vs 3; $p = 0.037$) with ulipristal acetate than with levonorgestrel.

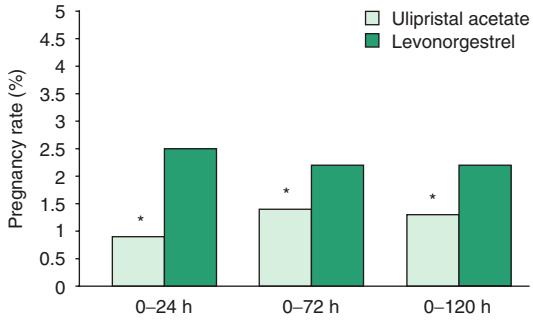

Fig. 2. Efficacy of ulipristal acetate versus levonorgestrel according to time from unprotected sexual intercourse to intake of emergency contraception. Results are for the efficacy evaluable population (n = 3445) in a *post hoc* meta-analysis of two randomized studies.[21,23]
* $p < 0.05$ vs levonorgestrel.

In a *post hoc* meta-analysis of data from these two studies[21,23] (see table I for design and results of individual trials) [n = 3445], the pregnancy rate was significantly ($p < 0.05$) lower with ulipristal acetate than with levonorgestrel at all timepoints within 120 hours of unprotected sexual intercourse (figure 2) [stratification accounted for interstudy differences].

5. Tolerability

Tolerability data on ulipristal acetate discussed in this section are derived primarily from clinical trials discussed in section 4. In all trials, ulipristal acetate was generally well tolerated and, where stated, the majority (89%[24] and 94%[23]) of adverse events were mild to moderate in severity and resolved spontaneously.

The most frequently reported treatment-related adverse events in recipients of ulipristal acetate (n = 1533) in an open-label, phase III trial were headache (9.3%), nausea (9.2%) and abdominal pain (6.8%).[24] Other common treatment-related adverse events in this study were dysmenorrhoea (4.1%), dizziness (3.5%) and fatigue (3.4%).

In the other phase III study (n = 2221), ulipristal acetate appeared to be as well tolerated as levonorgestrel.[23] The most common (occurred in ≥5% of patients) adverse events and their respective incidences (any cause) in ulipristal acetate or levonorgestrel treatment groups were headache (19% vs 18.5%), nausea (13% vs 11.5%), dysmenorrhoea (13% vs 14.5%), fatigue (5.5% vs 4%), abdominal pain (5% vs 6.5%) and dizziness (5% vs 4.7%) [data derived from a figure].[23]

While there was variation in the length of menstrual cycles during the study period compared with baseline, ulipristal acetate was generally associated with delayed onset of menses.[21,23,24] Mean menstrual cycle length increased by 2.1,[23] 2.6[21] and 2.8[24] days in ulipristal acetate groups, and the onset of menses was a mean of 1.2[23] and 2.1[21] days earlier than expected in levonorgestrel groups. The duration of bleeding during the

Table II. Modelled cost-effectiveness study of ulipristal acetate (UPA) compared with levonorgestrel (LNG) in women requesting emergency contraception within 120 hours of unprotected sexual intercourse (UPSI) in the UK.[26] The study was conducted from the perspective of the National Health Service and evaluated direct costs (2008 year of costing)

Drug	Cost (£)	Probability of pregnancy after UPSI (0–120 h) [%]	Cost of unintended pregnancy (£)	Drug administration costs[a] (£)	Total costs (£)	ICER (£)
UPA	16.95	1.28	12.13	52.95	65.08	311.00
LNG	5.37	2.20	20.85	41.37	62.22	

a Includes drug acquisition cost and cost of general practitioner visits.

ICER = incremental cost-effectiveness ratio.

menstrual period was not affected by ulipristal acetate.[23]

Following treatment with ulipristal acetate, intermenstrual bleeding (in most cases described as spotting) was reported by 8.7% of 1533 women compared with 3.3% before enrolment (based on previous 3 months).[24] In 100 women monitored before and after treatment with ulipristal acetate, there were no changes of clinical significance in complete blood count, hepatic and renal function, lipids and random glucose analyses.[24]

6. Pharmacoeconomic Considerations

A modelled, cost-effectiveness study in the UK compared the use of ulipristal acetate 30 mg versus levonorgestrel 1.5 mg in women requesting emergency contraception within 120 hours of unprotected sexual intercourse.[26] The perspective was that of the National Health Service and only direct costs (2008 year of costing) were considered. For those women who became pregnant despite treatment, possible outcomes were abortion, miscarriage or childbirth. Of these, childbirth carried the greatest cost (£2380), with a probability of 0.18, and abortion carried the greatest probability (0.66), with a cost of £672. Clinical input data were taken from two clinical trials that compared ulipristal acetate and levonorgestrel and a meta-analysis of combined data from these two trials (discussed in section 4).[21,23] The cost of adverse events was not considered as there was no difference in rates of adverse events between the two treatment arms in clinical studies (section 5).

The acquisition cost of ulipristal acetate is higher than that of levonorgestrel, but because the probability of pregnancy when the drug is taken within 120 hours of unprotected sexual intercourse was considered to be lower with ulipristal acetate, the difference in total costs between the two agents was only £2.86 in favour of levonorgestrel (table II). As a result, the incremental cost-effectiveness ratio (ICER) [i.e. the cost of preventing one additional unintended pregnancy] with ulipristal acetate versus levonorgestrel was £311, which was less than the estimated cost of an unintended pregnancy (£948).

In a sensitivity analysis that compared direct costs associated with the two drugs when taken within 72 hours of unprotected sexual intercourse, the ICER associated with ulipristal acetate was £500.[26]

As with all modelled analyses, this cost-utility study is a simplified simulation of reality and, therefore, subject to some limitations. For example, pregnancy rates were derived from a single meta-analysis of two randomized, head-to-head clinical trials, which demonstrated significantly lower pregnancy rates with ulipristal acetate than with levonorgestrel (section 4); however, both individual trials were noninferiority studies and were not powered to show superiority.

7. Dosage and Administration

A single tablet of ulipristal acetate 30 mg has recently been approved for emergency contraception within 120 hours of unprotected sexual intercourse or contraceptive failure in several countries, including the US[12] and the EU.[13] The tablet should be taken as early as possible, but no later than 120 hours following unprotected sex, and may be taken with or without food

(section 3.1). Ulipristal acetate is contraindicated in existing or suspected pregnancy, so pregnancy should be excluded before the drug is administered.[12,13]

Ulipristal acetate is designed as an occasional emergency contraceptive method and should not replace regular contraception.[12,13] The drug is not recommended for repeated use within the same menstrual cycle. A rapid return to fertility should be expected following treatment with ulipristal acetate, and regular contraception should be continued or initiated as soon as possible. Ulipristal acetate may reduce the contraceptive action of regular hormonal contraceptives (section 3.2), so a reliable barrier method of contraception during sexual intercourse in addition to continued use of the regular hormonal contraceptive is recommended until the start of the next menstrual period.

As no studies have been performed with ulipristal acetate in women with hepatic or renal impairment, there are no specific dosage recommendations for these populations,[12,13] except that the drug is not recommended in those with severe hepatic impairment in the EU.[13] Local prescribing information should be consulted for more details regarding contraindications, precautions and warnings.

8. Place of Ulipristal Acetate in Emergency Contraception

Emergency contraception is effective in preventing an unplanned pregnancy after unprotected sexual intercourse. Hormonal methods are used most commonly, largely because they are considered to be more convenient than the insertion of a copper-bearing intrauterine device.[4] Since gaining popularity in the 1960s, hormonal emergency contraception has continuously evolved to improve efficacy and reduce adverse effects.[6] Currently, the most commonly used hormonal agent is the progestin levonorgestrel. The recent introduction of ulipristal acetate provides the first of a new class of progesterone receptor modulators for emergency contraception.

Following unprotected sexual intercourse, pregnancy is likely to result only during the fertile period that extends from 5 days before ovulation to the day of ovulation.[4] Once released, the oocyte deteriorates rapidly to a point where fertilization is unlikely. During this 6-day period, fertility varies, with the probability of conception resulting from sexual intercourse estimated to range from 10% 5 days before ovulation to 33% on the day of ovulation.[27] As it is difficult to accurately predict the exact stage of the menstrual cycle at which unprotected intercourse occurred, emergency contraception is generally indicated at any time of the cycle.[28]

Hormonal methods generally prevent pregnancy by inhibiting or delaying ovulation. However, a full understanding of their respective modes of action remain somewhat limited.[4,15] Levonorgestrel acts by blocking or delaying LH surge and, therefore, its efficacy is dependent on administration prior to the onset of LH surge. Once the ovulatory process has been triggered, levonorgestrel is unable to prevent the follicle from rupturing to release the oocyte.[4,18]

In contrast, while ulipristal acetate is also thought to inhibit or delay LH surge if taken in the mid-follicular phase, if it is taken prior to ovulation and subsequent to LH surge, it may postpone LH peak. Thus, the principal action appears to be dependent on the time of the menstrual cycle that it is taken (section 2). Furthermore, ulipristal acetate is effective during the highly fertile phase immediately prior to ovulation when levonorgestrel is no longer effective in preventing follicular rupture. Ulipristal acetate may also have a direct effect of follicular rupture (section 2). Taken together, these results support the use of ulipristal acetate within an extended treatment window (120 hours) following unprotected sexual intercourse compared with levonorgestrel (72 hours).

Clinical trials in women requesting emergency contraception after unprotected intercourse demonstrated that ulipristal acetate is effective in preventing unplanned pregnancies, and it is no less effective than levonorgestrel in women presenting within 72 hours of unprotected intercourse (section 4). Across three clinical trials in this population of women, pregnancy rates with ulipristal acetate ranged from 0.9% to 2.1%; these rates

were significantly lower than estimated expected rates without emergency contraception (5–6%).[23,24] Furthermore, ulipristal acetate demonstrated sustained clinical efficacy throughout the 120-hour period after unprotected intercourse in which it is indicated.

In secondary efficacy analyses, ulipristal acetate was more effective than levonorgestrel in preventing pregnancies when administered late (within 72–120 hours) after unprotected intercourse, whereas there was no difference in efficacy for the total period (within 120 hours) [section 4]. However, the pregnancy rate was significantly lower with ulipristal acetate than with levonorgestrel when either agent was taken within 24, 72 or 120 hours of unprotected sexual intercourse in a *post hoc* meta-analysis of two clinical studies (section 4).[23] Data from the two studies, which were similarly designed and had the same primary endpoint, were combined to increase statistical power for comparing ulipristal acetate with levonorgestrel. Further data from clinical trials designed to show superiority may be warranted to confirm whether ulipristal acetate is more effective than levonorgestrel when administered within the first 72 hours postcoitus.

Ulipristal acetate was generally well tolerated in clinical trials, and appeared to be as well tolerated as levonorgestrel (section 5). Adverse events tended to be mild to moderate in severity and resolved spontaneously. The most frequent adverse effects associated with ulipristal acetate were headache, nausea and abdominal pain, with dysmenorrhoea, dizziness and fatigue occurring less commonly. There was some variation in menstrual cycle length, which generally increased by about 2–3 days in ulipristal acetate recipients (section 2), an effect that is consistent with the postponement of ovulation.

As with many new drugs, ulipristal acetate is more expensive than levonorgestrel. In a cost-utility study in the UK comparing direct costs of the two agents from a healthcare provider perspective, and based on clinical data from the meta-analysis (section 4), the cost of preventing one additional unintended pregnancy with ulipristal acetate compared with levonorgestrel (i.e. the ICER) was well within common willingness-to-pay thresholds when administered within 120 hours of unprotected intercourse and was lower than the estimated cost of an unintended pregnancy (section 6). In a sensitivity analysis, the ICER for ulipristal acetate versus levonorgestrel was higher when administered within 0–72 hours after unprotected intercourse, consistent with the improved efficacy that would be expected with levonorgestrel in this period compared with later (72–120 hours). Whether the use of ulipristal acetate will prove to be cost effective in other geographical regions remains to be seen.

Levonorgestrel is approved for use within 72 hours of unprotected sexual intercourse,[10] and its efficacy has been shown to wane over time.[8] In order to optimize efficacy, educational programmes have focused on the importance of accessing emergency contraception as soon as possible after unprotected sexual intercourse. The time-dependent efficacy was also a factor in making levonorgestrel easily available over-the-counter in many countries for women aged ≥17 years.[10] Data from clinical studies suggest that about 10–12% of women requiring emergency contraception present >72 hours after unprotected intercourse. Whether more women would present in this period if they knew that emergency contraception remained an option is unknown.

The search for effective and well tolerated emergency contraceptive measures is ongoing. Two potential alternatives include the cyclooxygenase-2-inhibitor meloxicam, which works by inhibiting prostaglandin synthesis, thereby suppressing ovulation and follicular rupture, and the anti-progestin gestrinone, which appears to inhibit implantation.[6] Ongoing clinical trials should help determine whether these agents will have a place in emergency contraception in the future.

In conclusion, ulipristal acetate is the first of a new class of selective progesterone receptor modulators, and it provides effective, sustained and well tolerated emergency contraception when taken within 120 hours after unprotected sexual intercourse or contraceptive failure. In clinical trials, the drug was no less effective than levonorgestrel when taken within 72 hours of unprotected

intercourse and was more effective when taken between 72 and 120 hours. Results of a meta-analysis suggest that ulipristal acetate may be more effective than levonorgestrel from day 1 and throughout the entire 5-day period following unprotected sexual intercourse. Unlike levonorgestrel, ulipristal acetate is able to prevent follicular rupture, potentially preventing pregnancy, when given in the advanced follicular stage of the menstrual cycle and, thus, provides a longer treatment window than levonorgestrel.

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