ulipristal acetate, 30mg tablet (EllaOne®) No. (599/10)
HRA Pharma UK Ltd

15 January 2010

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

ulipristal acetate (EllaOne®) is accepted for use within NHS Scotland for emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.

When administered within the licensed time frame for ulipristal or an active comparator for emergency hormonal contraception, contraceptive efficacy with ulipristal was non-inferior to that with the comparator in individual studies and statistically superior in a meta-analysis of two studies.

Other treatments are available at lower drug acquisition cost.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.

Dosing information

The treatment consists of one tablet to be taken orally as soon as possible, but no later than 120 hours (5 days) after unprotected intercourse or contraceptive failure. It can be taken at any moment during the menstrual cycle. If vomiting occurs within 3 hours of ulipristal intake another tablet should be taken.

Pregnancy should be excluded before ulipristal is administered.

Product availability date

1 October 2009

Summary of evidence on comparative efficacy

Ulipristal acetate is a synthetic selective progesterone receptor modulator with antagonistic and partial agonistic effects at the progesterone receptor. It inhibits or delays ovulation in a dose dependant fashion.

Efficacy of ulipristal has been studied in three randomised studies. One phase III non-inferiority study has compared ulipristal with levonorgestrel as emergency hormonal contraception (EHC) within 120 hours of unprotected intercourse (UPI), and the results have been combined in meta-analysis with those from a phase II study comparing ulipristal with levonorgestrel in a study of similar design. A second Phase III study was single-arm and assessed ulipristal in women presenting for EHC between 48 and 120 hours.

All trials recruited women aged over 16 or over 18 with regular menstrual cycles seeking EHC, and excluded those who were pregnant, breastfeeding, sterilised, using hormonal contraception or an IUD, or whose partners were sterilised. Pregnancy testing was performed at baseline and at regular intervals during follow-up until the occurrence of menses or confirmed pregnancy. In the absence of either after 60 days' follow-up, investigations for amenorrhoea were performed. The primary outcome was observed pregnancy rate. In the Phase III studies this was reported after exclusion from the analysis of women whose pregnancy status was unconfirmed or whose pregnancy was judged by an independent panel to be inconsistent with contraceptive failure e.g. if further intercourse had occurred post-treatment (modified intention-to-treat [mITT] population).

In each study, the observed pregnancy rate and its confidence intervals (CI) were compared to an estimated pregnancy rate that would be expected without the use of emergency contraception (EC). This was calculated for each study population by attributing a different risk of pregnancy to each day of the cycle. The observed rate was also compared to a clinical irrelevance threshold of 4% representing a 50% reduction from a hypothesised pregnancy rate of 8% estimated from previous reports. In the active-comparator studies there was also an assessment of non-inferiority of ulipristal to levonorgestrel, based on the difference in pregnancy rates between treatments.

In the phase III active-controlled single-blind study 2221 women were randomised to ulipristal micronised tablets 30mg or levonorgestrel 1.5mg, both as a single dose. The mITT group consisted of 1899 women, in whom there were 15 pregnancies in the ulipristal group and 25 in the levonorgestrel group. This corresponded to pregnancy rates of 1.6% (95% CI: 0.9% to 2.7%) and 2.6% (95% CI: 1.8%to 3.9%) respectively. An analysis of the trend in pregnancy up to 120 hours post UPI showed a sustained effect of ulipristal on pregnancy prevention. In a published interim analysis, for women treated within 72 hours of UPI, the pregnancy rate in the ulipristal group was 1.51% (95% CI 0.62% to 3.3%), meeting statistical criteria for efficacy.

The Phase II study showed that one 50mg capsule of ulipristal (pharmacokinetically equivalent to a 30mg micronized tablet) was non-inferior to 1.5mg of levonorgestrel given as two 0.75mg doses 12 hours apart. In the mITT population the pregnancy rate was 12/792 (1.5%) in the ulipristal group and 14/786 (1.8%) in the levonorgestrel group. The difference in pregnancy rates was -0.3% and the upper bound of the 97.5% CI was 1.42%. For the efficacy evaluable (EE) population, after exclusion of women with pre-treatment pregnancies and those using addition EC during treatment, there were fewer pregnancies in the ulipristal acetate group than in the levonorgestrel group - 7/775 (0.9%) vs. 13/774 (1.7%) with a difference of -0.8% (95% CI -2.4 to 0.77). The time-window for EHC intake after unprotected intercourse was 0-72 hours in this phase II study and 0-120 hours in the phase III comparative study. Otherwise the studies were similar in design and sufficiently homogeneous to combine the results in a meta-analysis. In this analysis (n=3445), the difference between ulipristal and levonorgestrel assumed statistical significance with an OR of 0.55 (95% CI: 0.32 to 0.93) for women presenting within 120 hours of UPI.

In the single-arm phase III study with ulipristal 30mg started between 48 and 120 hours after UPI, the mITT population consisted of 1241 women with 26 pregnancies giving an overall pregnancy rate of 2.1% (95% CI: 1.4% to 3.1%). The upper limit of the 95% CI was significantly lower than the expected pregnancy rate in this study (5.5%) as well as the clinical irrelevance threshold. There was no evidence of a change in efficacy over time from intercourse to EHC when pregnancy rates were analysed by 24-hour time intervals in a logistic regression model.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

In the Phase III active-comparator study, adverse events were reported by 597 (54%) and 626 (56%) of women in the ulipristal and levonorgestrel groups respectively, with just under half being considered treatment-related. The majority (93% with ulipristal and 94% with levonorgestrel) were mild to moderate in intensity. The most frequently reported adverse events were similar for both groups and included headache, dysmenorrhoea, nausea, fatigue, dizziness and abdominal pain. Two serious adverse events were judged possibly related to EHC use; one case of dizziness following ulipristal (resolved within 24 hours) and a molar pregnancy after levonorgestrel.

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

The only licensed alternative to ulipristal for EHC is levonorgestrel 1.5mg, which is licensed for administration up to 72 hours after UPI while ulipristal is licensed for administration up to

120 hours afterwards. Current guidance suggests that levonorgestrel may be considered for EHC between 72 and 120 hours but women should be informed of the limited evidence of efficacy and that such use is outwith licence. An alternative option for EC, that can be offered after 72 hours, is an intra-uterine device. However this is an invasive, long-term form of contraception and uptake is relatively low.

The meta-analysis used mITT data from the Phase III study and EE data from the Phase II study. This may have influenced the odds ratio reported since the rate of pregnancy in the Phase II study was lower in the EE population than for mITT, particularly for ulipristal. However, the definition of mITT in the Phase III studies differed from that in the Phase II study and had more in common with the EE population in that study.

In the single-arm phase III study in which ulipristal could be given at any time between 48 and 120 hours after UPI, numbers were fairly evenly distributed before and after the 72-hour interval, and logistic regression analysis by 24-hour periods suggested no falling off of efficacy over time.

In the Phase III comparative study, treatment with ulipristal was associated with an increase of about two days in menstrual cycle length, reflecting its mode of action in delaying ovulation. Levonorgestrel was associated with a slightly early onset of menses with no effect on cycle length.

Levonorgestrel is available for EHC as a prescription only medicine (POM) and as a pharmacy (P) preparation, allowing supply through prescription, patient group direction or over-the-counter sale. Ulipristal is classified as a POM.

*Other data were also assessed but remain commercially confidential.**

Summary of comparative health economic evidence

The manufacturer presented a cost-effectiveness analysis of ulipristal versus levonorgestrel in two scenarios: first, for all women presenting up to 120 hours and second, for all women presenting up to 72 hours. The time horizon for the economic analysis was 9 months so as to include the length of time for a pregnancy to reach full term. A comparison for the period 72-120 hours alone would have been of interest but less than 10% of the patients in the comparative clinical studies fell into this category so the numbers were too small. The emergency intra-uterine device was not considered as a possible comparator on the basis of low uptake, the need for insertion by a skilled health care professional and the fact that benefits are long-term and not easily comparable with a one time method such as EHC.

A decision tree approach was used, using data from the main clinical studies. Other costs considered included General Practitioner consultation for the prescription, plus the NHS costs of an unintended pregnancy - including terminations, miscarriages and deliveries. These were valued using NHS Reference Costs from England which was an acceptable source. The submission stated that for the period 0-120 hours after unprotected intercourse, the added cost per unintended pregnancy averted was £390 (based on added cost of £3.59 for a reduction in pregnancy rate of 0.92%). The comparable result in the submission for the period 0-72 hours after unprotected intercourse was £579.

The main concern was the use of unintended pregnancy averted as a measure of benefit creating problems in terms of ensuring consistency of SMC decision-making with other medicines, but this is an accepted outcome measure in economic evaluations of contraceptives.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Brook
- Family Planning Association (FPA)
- British Pregnancy Advisory Service (BPAS)

Additional information: guidelines and protocols

The Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit, supported at that time by the University of Aberdeen and the Scottish Programme for Clinical Effectiveness in Reproductive Health (SPCERH) provided guidance on guidance on Emergency Contraception in April 2006. It made the following recommendations:

- Levonorgestrel should be given as a single 1.5 mg dose as soon as possible after UPI, and within 72 hours
- Levonorgestrel may be considered for EHC between 73 and 120 hours after UPI, but women should be informed of the limited evidence of efficacy and that such use is outside the product's licence.*
- An IUD (or advice on how to obtain one) should be offered to all women attending for emergency contraception even if presenting within 72 hours of UPI.

* The Summary of Product Characteristics for levonorgestrel as EC (Levonelle 1500) advises that it should be taken as soon as possible, preferably within 12 hours and no later than 72 hours, after UPI.

The Royal Pharmaceutical Society of Great Britain issued practice guidance on the supply of emergency hormonal contraception as a pharmacy medicine in September 2004. It describes three possible routes by which women can obtain EHC: as a pharmacy (P) medicine; as a prescription-only medicine (POM) via primary care, family planning, hospital genito-urinary medicine clinics, or some accident and emergency centres; and as a POM through patient group directions, via NHS Walk-in Centres, family planning clinics and some community pharmacies.

Additional information: comparators

Levonorgestrel is the only other licensed medicine available for EHC. Intrauterine devices (IUD) may be used for EC but are invasive and represent a long-term method of contraception and are also unlicensed for this indication.

Cost of relevant comparators

Drug	Dose regimen	Cost per course (£)
Ulipristal	**One 30mg tablet**	**£16.95**
Levonorgestrel (Levonelle® 1500)	One 1.5mg tablet	£5.37

Levonorgestrel as Levonelle One Step® may be sold to women aged >16 years. Levonelle 1500 is the POM preparation. Doses are given for one episode of EC, are for general comparison and do not imply therapeutic equivalence. A second dose of either agent may be given in the event of vomiting within three hours of administration. Costs from eVadis on October 28 2009.

Additional information: budget impact

The manufacturer provided estimates of the total cost of EHC prescribing (ulipristal and levonorgestrel combined) under different scenarios, ranging from £150k in year 1 if ulipristal were used for women presenting after 72 hours to £196k if ulipristal were used for women presenting after 48 hours. The net impact of ulipristal would be £22k-24k per year if it was restricted to 72-120 hours and £66k-73k per year if it was restricted to 48-120 hours, depending on the proportion of levonorgestrel that is dispensed as Levonelle One Step®.

The manufacturer estimated 40,491 to 48,589 women would require EHC in 2010 with the figures falling very slightly over time as the demographic structure of the Scottish population changes. Around 43% of these women were assumed to require a prescription therefore 21,031 women would be potentially eligible for ulipristal. Based on the single-arm phase III study 10% of women present 4 or 5 days after unprotected sex, so if ulipristal was reserved for 72-120 hours, 2,103 women would be eligible. If ulipristal was restricted to 48-120 hours it was assumed 30% of women would be eligible.

The estimates assumed 100% market share within the restrictions (after 72 hours or after 48 hours).

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including ***04 December 2009.***

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/*

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Creinin MD, Schlaff W, Archer DF, et al. Progesterone receptor modulator for emergency contraception: a randomized controlled trial. Obstetrics and Gynecology 2006;108:1089-97.

Fine P, Mather H, Ginde S et al. Ulipristal Acetate as Emergency Contraceptive Taken 48 to 120 hours after Unprotected Intercourse. *Obstetrics and* Gynecology *in press, February 2010.*

European Medicines Agency. CHMP Assessment Report for Ellaone (ulipristal acetate). EMEA/261787/2009. www.emea.europa.eu. Accessed October 2009.