Northern Treatment Advisory Group

Efficacy of emergency contraception in women over 75Kg

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Summary

- Manufacturer-initiated changes to the summaries of product characteristics of levonorgestrel emergency contraception (EC) products marketed in Sweden and Ireland prompted a EU-wide review of the available evidence on the effect of bodyweight on efficacy of all oral EC products.

- The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) completed the review in July 2014.

- The EMA considered data on the relationship between bodyweight and EC efficacy from three meta-analyses of studies of levonorgestrel, ulipristal or both.

- The CHMP concluded that the data available are too limited and not robust enough to conclude with certainty that contraceptive effect is reduced with increased bodyweight and recommended that statements on the impact of bodyweight should be deleted from product information.

- The Clinical Effectiveness Unit of the Faculty of Sexual and Reproductive Healthcare of the Royal College of Gynaecologists and Obstetricians issued a statement in support of the conclusions of the EMA review in July 2014. The statement emphasises that: "*Healthcare professionals should continue to remind women that emergency contraception is an occasional 'rescue' method and should not replace a regular contraceptive method*" and that "*Irrespective of body weight, all women requesting emergency contraception should be informed that the copper intra-uterine device, Cu-IUD is the most effective method of EC, with an estimated failure rate considerably less than 1%*."

- Although the European regulatory authority has determined that there is insufficient evidence to justify altering EC product information or making recommendations based on bodyweight, the North of England Treatment Advisory Group may wish to consider providing additional advice to patients, prescribers and commissioners.

Introduction and background

In July 2014 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) completed a review of emergency contraception (EC) requested in January by the Swedish medicines regulatory agency (Lakemedelsverket) under Article 31 of Directive 2001/83/EC.[1,2]

The Article 31 request followed approval of manufacturer-initiated changes to the Swedish and Irish summaries of product characteristics (SPCs) for NorLevo® (HRA Pharma), an EC product containing levonorgestrel (both 0.75mg and 1.5mg tablets are licensed). The Swedish and Irish SPCs were amended to include statements that: *in clinical trials, contraceptive efficacy was reduced in women weighing 75 kg or more and levonorgestrel was not effective in women who weighed more than 80 kg*.[2] No other manufacturers have requested changes to product information. HRA Pharma do not market a levonorgestrel containing EC product in the UK; the SPCs for UK authorised levonorgestrel EC products were not amended and have never included any cautions about body weight. The only EC product marketed by HRA Pharma in the UK contains the selective progesterone receptor modulator, ulipristal (ellaOne®).[3]

The EU-wide review assessed whether bodyweight affects the effectiveness of levonorgestrel or ulipristal for EC and whether the statements added to the NorLevo® SPC should be included in the product information for other emergency contraceptives. The CHMP concluded that ***the data available are too limited and not robust enough to conclude with certainty that contraceptive effect is reduced with increased bodyweight*** and recommended that the statements on the impact of bodyweight should be deleted from the NorLevo® product information. Both levonorgestrel and ulipristal EC products *can continue to be used in women of all weights as the benefits are considered to outweigh the risks*. The CHMP also recommended that the results of studies which informed the assessment should be included in all relevant EC product information.[1]

The World Health Organisation, the US Food and Drug Administration, New Zealand Medsafe and the Therapeutic Goods Administration in Australia are also currently reviewing the available data on the effect of bodyweight on the efficacy of emergency contraception.[4-6] The Canadian regulator, Health Canada, announced in March 2014 – following a submission from HRA Pharma – that manufacturers of all levonorgestrel products marketed in Canada had been asked to change product literature to indicate reduced efficacy in women weighing 75-80Kg and lack of efficacy in women over 80Kg.[7]

Although the European regulatory authority has determined that there is insufficient evidence to justify altering EC product information or making recommendations based on bodyweight, the North of England Treatment Advisory Group may wish to consider providing additional advice to patients, prescribers and commissioners.

Clinical evidence

EMA Review[1]

The EMA considered data on the relationship between bodyweight and EC efficacy from three meta-analyses of studies of levonorgestrel, ulipristal or both. A version of one of the meta-analyses, based on two published studies comparing ulipristal to levonorgestrel, has been published.[8-10A] Analysis of these two studies is cited in NorLevo® product information as the source of data demonstrating a relationship between bodyweight and levonorgestrel efficacy.[11] However, the original published figures differ from those in the EMA review, as the EMA re-analysed the levonorgestrel data and excluded off-label use (more than 72 hours after unprotected sex) [LNG-1]. The results of the other two meta-analyses are only available in summary form from the EMA. The first of these two examined the effects of bodyweight on the efficacy of levonorgestrel across three published placebo-controlled trials sponsored by the World Health Organisation [LNG-2];[12-14] the second analysed the effects of bodyweight on the efficacy of ulipristal across four studies included in the marketing authorisation application and European Public Assessment Report for ellaOne® (these four included the two published levonorgestrel comparison studies above) [UPA].[9,10,15]

The pregnancy rates reported in the EMA review for women in three bodyweight categories are shown in table 1 below.[1]

Table 1: Pregnancy rates by bodyweight category (EMA)

	PREGNANCY RATE (95% Confidence Interval)		
BMI (Kg/m^2)	**LNG-1** [data from 2x levonorgestrel vs uliprisal comparison studies]	**LNG-2** [data from 3x WHO placebo-controlled studies]	**UPA** [data from 4x regulatory submission studies]
18.5-25	0.96% (0.44-1.82)	0.99% (0.70-1.35)	1.23% (0.78-1.84)
25-30	2.36% (1.02-4.60)	0.57% (0.21-1.24)	1.29% (0.59-2.43)
≥30	5.19%# (2.62-9.09)	1.17% (0.24-3.39)	2.57 (1.34-4.45)

 # - statistically significantly different from BMI 18.5-25 within treatment group

[A] A summary of the results of the published analysis was included in an updated appraisal document prepared for the former North East Treatment Advisory Group (NETAG) in December 2012. The update was prepared following the rejection in November 2012 of an appeal against a decision on ulipristal reached in October 2009. The group considered the updated appraisal and an application to recommend ulipristal for specific patient groups (including women with BMI values above a certain threshold) in January 2013, but was not satisfied that the new evidence adequately and reliably demonstrated superiority of ulipristal in those groups. The group did not recommend ulipristal for any specific patient groups or make any changes to the recommendations made in October 2009.

The EMA noted the following:

- LNG-1
  - Primarily Caucasian women.
  - Reduced contraceptive effect observed with increased bodyweight/BMI.
- LNG-2
  - Primarily African and Asian women.
  - No trend for reduced efficacy with increased bodyweight/BMI.
- UPA
  - Possible trend for reduced efficacy with increased bodyweight/BMI, but confidence intervals overlap.

The EMA have not published further details of any of the three meta-analyses. Only the published post-hoc analysis linked to the first of the EMA meta-analyses [LNG-1] is available for further consideration (Glasier et al. 2011).

Glasier et al. 2011 post-hoc analysis[8]

The 2011 post-hoc analysis combined data from two non-inferiority studies designed to compare the efficacy of levonorgestrel to ulipristal.[9,10] Neither study was designed to investigate the effects of bodyweight on efficacy; the original trial reports do not mention bodyweight or BMI and it is not clear how the data on bodyweight were collected. Subsequent commentary (based on communication with HRA Pharma) suggests that around half of the women in these studies self-reported their weight and notes that such reports may be unreliable.[16]

The first of the two studies (Creinin et al. 2006) was double-blind, recruited women with regular menstrual cycles who requested EC within 72 hours of unprotected sex and compared the efficacy of two doses of levonorgestrel 0.75mg taken 12 hours apart to a single dose of ulipristal 50mg plus a placebo 12 hours later. No products providing these doses are currently available in the UK. All levonorgestrel EC products available in the UK provide 1.5mg as a single dose. The ulipristal EC product ellaOne® provides 30mg as a single dose.[9]

The second study (Glasier et al. 2010) was single-blind (investigators aware of allocation), recruited women with regular menstrual cycles who requested EC within 120 hours of unprotected sex and compared single doses of levonorgestrel 1.5mg and ulipristal 30mg, given under direct supervision. Levonorgestrel 1.5mg tablets are not licensed for use beyond 72hours after unprotected sex. Women presenting between 72hours and 120hours after unprotected sex were initially offered an intrauterine device (unless contraindicated). Randomisation was stratified by time from unprotected intercourse.[10]

The post-hoc analysis of the two studies investigated the relationship between EC efficacy and the following variables: age; body mass index (BMI); time (hours) from unprotected intercourse to treatment with EC; occurrence of further acts of unprotected intercourse (after use of EC); history of pregnancy, and; conception probability. Data for women who received EC and for whom pregnancy status at follow up was known were included. Three of the six covariates assessed in a

nominal logistic model were found to have a statistically significant effect on the risk of pregnancy: BMI; conception probability, and; further intercourse. Pregnancy rates reported are shown in table 2 below.[8]

Table 2: Pregnancy rates by bodyweight category (Glasier et al.)

	PREGNANCY RATE (95% Confidence Interval)		
BMI (Kg/m^2)	**LNG**	**UPA**	**OVERALL**
<25	1.3% (0.8-2.2)	1.1% (0.6-1.9)	1.2% (0.8-1.8)
25-30	2.5% (1.3-4.6)	1.1% (0.4-2.7)	1.7% (1.0-3.0)
≥30	5.8%# (3.5-9.5)	2.6% (1.2-5.6)	4.3%# (2.8-6.5)

 # - statistically significantly different from BMI 18.5-25 within treatment group

The data was then re-analysed with weight substituted for BMI as a covariate in the logistic regression model. Weight was also found to have a statistically significant effect on the risk of pregnancy ($p<0.0001$).

The authors report that a restricted spline cubic smoothing model was applied to the nominal logistic regression model to better describe the relationship between covariates and risk of pregnancy. This analysis suggested that pregnancy rates increased with increasing body weight for both levonorgestrel and ulipristal and that rates reached those expected among women not using EC at different threshold values (26Kg/m^2 or 70Kg for levonorgestrel; 35kg/m^2 or 88Kg for ulipristal). Neither the EMA nor Health Canada commented on the suitability or reliability of this advanced statistical technique for unplanned analysis of the relationship between bodyweight and pregnancy rate.[1,7]

Guidelines and professional body recommendations

Several professional societies have considered the implications of the manufacturer-initiated changes to NorLevo® product information, including Sexual Health and Family Planning Australia, the European Consortium for Emergency Contraception, the European Society of Contraception and Reproductive Health and the Faculty of Sexual and Reproductive Healthcare of the Royal College of Gynaecologists and Obstetricians (FSRH). Some of these bodies, including the FSRH, published updated guidance and advice (including a guide for community pharmacists operating under PGD) before the EMA completed its review.[17-19] The updated FSRH EC guidance concluded that more research was required before specific obesity-related recommendations could be made. Subsequently, the Clinical Effectiveness Unit (CEU) of the FSRH issued an extra statement in support of the conclusions of the EMA review in July 2014.[20] The statement emphasises that: "*Healthcare professionals should continue to remind women that emergency contraception is an occasional 'rescue' method and should not replace a regular contraceptive method*"

and that "*Irrespective of body weight, all women requesting emergency contraception should be informed that the copper intra-uterine device, Cu-IUD is the most effective method of EC, with an estimated failure rate considerably less than 1%*." The CEU document includes advice on what to tell women seeking EC and a Question and Answer section for healthcare professionals.

The MHRA have also issued additional advice for healthcare professionals. A letter from the deputy director of the MHRA to UK healthcare professionals makes the following points:[21]

- Levonorgestrel and ulipristal acetate can be used for emergency hormonal contraception regardless of the woman's weight or BMI.
- Emergency contraceptives should be taken as soon as possible after unprotected sexual intercourse or contraceptive failure.
- Emergency contraceptives do not prevent pregnancy in every instance.
- Emergency contraception is for use, as the name suggests, in an emergency. It should not be used to replace a regular contraceptive method.
- Levonorgestrel containing emergency contraceptives work best if taken within 12 hours of unprotected sexual intercourse or contraceptive failure but can prevent pregnancy if taken up to 3 days afterwards.
- Ulipristal acetate containing contraceptives can prevent pregnancy if taken up to 5 days after unprotected sexual intercourse or contraceptive failure.

Cost analysis

During the financial year 2013/14, almost £55,500 was spent on just under 8,000 prescriptions for oral emergency contraception dispensed on behalf of primary care prescribers in the CCGs in the North East and Cumbria (equivalent to £1,720 and 247 prescriptions per 100K population per annum). 67% of this sum was spent on just over 6,800 prescriptions for levonorgestrel (86% of total prescriptions). Figures for North Cumbria (excluding Barrow-in-Furness and South Lakeland districts), Hambleton District and Richmondshire District are not directly available. However, the aggregate figure for the North East and Cumbria (including Barrow and South Lakeland) is likely to be a reasonable approximation for the NTAG footprint (population of Hambleton and Richmondshire districts is approximately 30,000 lower than that of Barrow and South Lakeland districts = 0.9% of total population).[22,23]

Detailed data on provision of emergency contraception via community services commissioned by local authorities (LA) (e.g. family planning clinics, specialist sexual health services and provision by community pharmacists operating under patient group directions) are not currently available. Aggregate national data on provision via contraception clinics suggest that around 230 women per 100,000 population received oral EC via contraception clinics during 2012/13.[24] Sample data from the North of Tyne LAs suggest that around 500 to 2,900 women per 100,000 population received oral EC via LA funded community pharmacy schemes during 2013/14 (between c.50% and almost 90% of all EC provided).[25]

Hence, up to 3,400 women per 100K might receive oral EC via primary care prescription or LA provision (contraception clinic or community pharmacy PGD) each year.

Data on provision of intra-uterine devices (IUDs) for emergency contraception are only available at aggregated national level.[24] These indicate that approximately 5% of women attending LA commissioned community contraception clinics for emergency contraception receive IUDs. This figure is likely to include women referred from community pharmacies and some GP surgeries.

Approximately one quarter of women in the North East, Cumbria and North Yorkshire have a BMI>30Kg/m^2 (obese).[26] There are no published data on the proportion of sexually active pre-menopausal women with BMI>30, but the figure is likely to be lower. There are no reliable data on the proportion with bodyweight > 80Kg or with bodyweight between 75Kg and 80Kg.

NHS prices for EC (August 2014) are:[27]

levonorgestrel 1.5mg – £5.20 per tablet

ulipristal 30mg - £16.95 per tablet

Quoted prices for provision of intrauterine contraception via General Practice Locally Enhanced Services vary from £75.50 to £105 per insertion. Prices vary, but the average price for prescribed IUDs during 2013/14 was £11.30.[22] Equivalent data for LA commissioned services are not currently available.

If women with BMI>30Kg/m^2 were to choose IUDs over oral emergency contraception, costs could rise by up to £80,000 per 100,000 population per annum (circa £2.6 million across the entire NTAG footprint). It is likely that the majority of this additional cost would be born by Local Authority commissioned services. The benefit obtained via increased use of IUDs (e.g. extended contraceptive cover) is difficult to quantify, but IUDs are a more reliable method of EC and NICE have determined that all long-acting reversible methods of contraception are likely to be more cost-effective than user-dependent methods.

Patient impact

Changes in commissioning arrangements for emergency contraception in recent years have greatly improved access. Convenience, flexibility and timeliness are likely to be valued by women and may contribute to greater overall effectiveness. The majority of women requiring emergency contraception now access NHS provision via community pharmacists operating under patient group directions. Data from contraception clinics – which will receive referrals from other agencies as well as attending to women who access their services directly – suggest that a very small proportion of women requesting emergency contraception opt for intra-uterine devices, despite being counselled about greater efficacy. As IUDs require placement by a specialist or a specially trained GP, this method of EC may be difficult for some women to access within the 5-day timeframe required. Many women are likely to prefer the convenience and simplicity of oral methods even if this entails a higher risk of pregnancy. Women need straightforward, personalised accurate information on the advantages and disadvantages – and uncertainties – associated with all methods of emergency contraception in order to help them make choices.

Points to consider

The EMA have determined that available data are too limited and not sufficiently robust to draw reliable conclusions about the relationship between bodyweight and EC efficacy.

The EMA have advised that the balance of risk and benefit favours continued availability of all forms of oral EC for women irrespective of bodyweight.

The EMA have recommended that statements regarding the influence of bodyweight on the efficacy of levonorgestrel should be removed from European product literature.

The EMA have also recommended that the results of the studies which informed the CHMP assessment should be included in European literature for all EC products.

No studies have prospectively investigated the effects of bodyweight on EC efficacy.

Data on bodyweight collected during studies comparing levonorgestrel to ulipristal may not be reliable.

Data on the relationship between bodyweight and EC efficacy are conflicting.

Nonetheless, it remains possible that both levonorgestrel and ulipristal may be less effective at preventing pregnancy in women with BMI>30.

The FSRH advise healthcare professionals to inform all women requesting emergency contraception that the copper intra-uterine device is the most effective method of EC, with an estimated failure rate considerably less than 1%.

The FSRH also advise that decisions about which EC to offer a woman should take account of personal preference and the degree of risk which she is prepared to accept. Discussions should cover efficacy of different methods, adverse effects, interactions, medical eligibility and need for additional contraceptive precautions.

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