EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report

For Emergency contraceptive medicinal products containing levonorgestrel or ulipristal

INN/active substance: levonorgestrel, ulipristal

Procedure number: EMEA/H/A-31/1391

ellaOne EMEA/H/A-31/1391/C/1027/0028

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 16 January 2014, Sweden triggered a referral under Article 31 of Directive 2001/83/EC. The CHMP was requested to give its opinion on whether the marketing authorisations for emergency contraceptives medicinal products containing levonorgestrel or ulipristal should be maintained, varied, suspended or withdrawn.

The procedure described in Article 32 of Directive 2001/83/EC was applicable.

2. Scientific discussion

2.1. Introduction

Emergency contraceptives are medicinal products that can be used to prevent an unintended pregnancy following an unprotected sexual intercourse or in case of failure of a contraceptive method. Available products in the EU contain either levonorgestrel (LNG) or ulipristal acetate (UPA). The products act by inhibiting and/or delaying ovulation.

LNG is a synthetic progestagen. For emergency contraception one tablet of 1.5 mg LNG needs to be taken, or two tablets of 0.75 mg LNG at once. The products are indicated for emergency contraception within 72 hours (3 days) of unprotected sexual intercourse or contraceptive failure, and have been approved in more than 100 countries worldwide and used for more than 30 years. LNG-containing emergency contraceptives are available as over-the-counter (OTC) medicinal products in several European countries.

UPA (30 mg) (ellaOne) is an orally active synthetic progesterone receptor modulator, which acts via high affinity binding to the human progesterone receptor. The product is indicated for emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure. UPA has been approved for emergency contraception in 73 countries and is marketed in 55 of them. UPA has been administered to more than 1.4 million women worldwide.

In November 2013, for one of the LNG-containing products (Norlevo) a mutual recognition variation procedure was finalised. The outcome of that procedure was that information was included in the product information regarding the effect of the woman´s body weight on the effect of the product. Contraceptive efficacy was reduced in women weighing 75 kg or more, and LNG was not effective in women who weighed more than 80 kg. These revisions were based on analyses of two clinical studies (HRA2914-507 and HRA2914-513) primarily intended to demonstrate the efficacy of UPA acetate as an emergency contraceptive and in which LNG was used as an active comparator.

Furthermore in a post-hoc analysis of pregnancies in the LNG group, the effect of body weight on pregnancy rate was analysed. The analysis is also described in a published paper (Glasier et al., 2011)[1], in which BMI (body mass index) was the co-variate primarily analysed. The authors concluded that women with a BMI above 25 kg/m^2 will have an increased risk of pregnancy upon use of LNG as an emergency contraceptive compared to women with a BMI below 25 kg/m^2.

The ability of LNG-containing emergency contraceptives to prevent an unintended pregnancy seems to be impaired with increasing body weight and/or BMI (body mass index). Other LNG-containing emergency contraceptives have no information included in the product information with respect to

1 Glasier A et al.: Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel, Contraception (2011); 84, 363–367

reduced efficacy at increased weight/BMI. Since LNG-containing emergency contraceptive products are available as over-the-counter (OTC) medicinal products in several Member States, it is particularly important to review all available clinical data related to this issue, with the view that the correct information reflecting the existing clinical data is available to women.

For UPA, a similar effect of increasing weight/BMI on the efficacy cannot be excluded and further evaluation is needed. Currently, for UPA no information regarding the woman´s weight or BMI is included in the product information. Corresponding analyses have, however, been performed for UPA and are published by Moreau and Trussell (2012)[2], where it is concluded that the pregnancy rate was higher in obese women (BMI ≥ 30 kg/m2 or weight > 85 kg) compared with women of normal weight or BMI.

Based on the above considerations for both INNs, on 16 January 2014 the Swedish Agency sent a notification for a referral under Article 31 of Directive 2001/83 EC regarding all emergency contraceptives containing LNG or UPA, asking the CHMP to give its opinion on whether the marketing authorisations should be maintained, varied, suspended or withdrawn.

2.2. Clinical aspects

2.2.1. Clinical pharmacology

2.2.1.1. PK for LNG

There are no pharmacokinetic (PK) studies on orally administered LNG-only, which evaluated effect of body weight. However during this procedure, data are discussed that were extracted from PK studies performed with combined oral contraceptives. After administration of combined oral contraceptives (LNG + ethinylestradiol) obese women (BMI >30) showed a lower LNG C_{max}, a lower AUC_{0-24h} and an increased terminal half-life, but comparable trough levels. The differences in PK might be explained by altered distribution and slower elimination due to the lipophilic characteristics of LNG.

2.2.1.2. PK/PD for LNG

The relationship between pharmacokinetics and delay of ovulation is not clear and the minimum required plasma concentration of LNG-only for adequate efficacy after a single dose as an emergency contraceptive (EC) is unknown.

For combined oral contraceptives, containing LNG in combination with ethinylestradiol it was concluded that the steady state plasma levels of LNG in obese women are still well above the minimum effective concentration needed for adequate suppression of ovulation. For LNG-only used as emergency contraceptives this has not been established.

Based on a study by Croxatto and colleagues (2004)[3]it can be concluded that the minimum required LNG concentration for adequate delay of ovulation is probably much lower than the usually observed concentrations of a standard 1.5 mg dose for emergency contraception. In this study, it was observed that a single dose of 0.75 mg LNG as emergency contraceptive was at least as effective as the currently used standard 1.5 mg dose for delay of ovulation in the 5-day period needed for emergency contraceptive effectiveness, despite that the C_{max} and AUC of LNG were about 50% lower. Very early

2 Moreau C, Trussell J. Results from pooled Phase III studies of ulipristal acetate for emergency contraception. Contraception, (2012) Dec; 86(6):673-80.

3 Croxatto HB, Brache V, Pavez M, Cochon L, Forcelledo ML, Alvarez F, Massai R, Faundes A, Salvatierra AM. Pituitary-ovarian function following the standard levonorgestrel emergency contraceptive dose or a single 0.75-mg dose given on the days preceding ovulation. Contraception. (2004);70(6):442-50.

publications on the minimal effective dose report that even a single dose of 0.4 mg LNG could be sufficient (Kesseru et al., 1974)[4].

Therefore, the treatment with an emergency contraceptive with 1.5 mg LNG may still result in appropriate effectiveness in obese women, despite the differences in PK between normal weight and obese women.

2.2.1.3. PK for UPA

It is unknown if the pharmacokinetic and pharmacodynamic properties of UPA are different between normal weight and obese women.

2.3. Clinical efficacy

Obesity is a known risk factor for subfertility during anovulation. Current fertility guidelines (NICE, 2013) therefore also recommend that women who have a BMI of 30 or over and who are not ovulating should be informed that losing weight is likely to increase their chance of conception. Also when a woman is ovulating with a BMI of 30 or over, the recommendation is to inform her that she is likely to take longer to conceive. In the emergency contraceptive studies only women with regular menstrual cycles are included.

Van der Steeg and colleagues (2008)[5] evaluated the spontaneous pregnancy chances in subfertile, ovulatory women. By analysis of 3029 subfertile couples, the authors found that the probability of a spontaneous pregnancy declined linearly with a BMI over 29 kg/m^2. Corrected for possible related factors, women with a high BMI had a 4% lower pregnancy rate per kg/m^2 increase [hazard ratio: 0.96 (95% CI 0.91–0.99)]. The results indicate that obesity is associated with lower pregnancy rates in subfertile ovulatory women. Although this study was performed in subfertile, ovulatory women, it could be expected that in the general population of women, there will also be a trend for a decrease in pregnancy chance with an increasing BMI of 30 and over.

2.3.1. Efficacy for hormonal contraceptives

A Cochrane analysis (Lopez et al., 2013)[6] on hormonal contraceptives for contraception in overweight or obese women found nine reports with data from 13 trials. Five reports from 2002 to 2012 compared BMI groups; of those, one reported a higher pregnancy risk for overweight or obese women. In the other four studies the comparisons reported were not significantly different for pregnancy. Further, the investigators did not see any trends when they examined deciles for weight and BMI in these four studies. Lopez and colleagues (2013) concluded that the evidence did not generally show an association of BMI with effectiveness of hormonal contraceptives.

2.3.2. Efficacy for emergency contraceptives

In the case of emergency contraception, efficacy was demonstrated initially in non-comparative observational studies, since the use of placebo was felt to be unethical. Therefore, the chance that pregnancy would occur in the absence of emergency contraception is estimated indirectly using published data on the probability of pregnancy on each day of the menstrual cycle. The effectiveness of

4 Kesserü E, et al. The hormonal and peripheral effects of d-norgestrel in post-coital contraception. Contraception. (1974);10(4):411-24.

5 van der Steeg JW et al. Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. Hum Reprod. (2008) Feb;23(2):324-8.

6 Lopez LM et al. Hormonal contraceptives for contraception in overweight or obese women. Cochrane Database Syst Rev. (2013) Apr 30;4

emergency contraception has been estimated by comparing the observed number of pregnancies with the number of pregnancies expected in the absence of treatment.

According to the most common method, the expected number of pregnancies is estimated by multiplying the number of treated women who had unprotected intercourse, on each cycle day relative to the expected day of ovulation, by external estimates of the probability of conception resulting from unprotected intercourse on that cycle day.

In the early 60's, Tietze estimated that the chance of pregnancy with one completely random act of intercourse was 2% to 4%. More recently, Holmes and her colleagues reported that the probability of pregnancy after rape was 5% in a national sample of US women. A specific approach frequently used for the purpose was suggested by Dixon and colleagues. Dixon created a single set of pregnancy rates from several published studies (Barett, 1969; Holmes, 1996; Vollman, 1977). An arbitrary error distribution was added to account for the biologic variability of ovulation day. With Dixon's method, 14 days are subtracted from a woman's usual cycle length to estimate the "usual cycle day of ovulation". Dixon's pregnancy rates are then applied to the intercourse day relative to this inferred cycle day of ovulation. Women with irregular cycles were excluded from the study.

Trussel and colleagues (1998)[7] derived estimated conception probabilities by cycle day from two datasets (British and North Carolina trials, representing 237 pregnancies out of 1027 ovulatory cycles) on the outcomes of a trial in which 4136 women were enrolled. (These datasets include only clinical pregnancies and exclude those diagnosed by biochemistry only, and thus not likely to be recognized as pregnancy by the patients.) The authors assigned non-zero estimated conception probabilities to cycle days -5 to +1 (relative to day of ovulation).

Although several further modifications or new estimations of these probabilities have been published since then, the Trussell 1998 method is the most frequently used one. As estimated pregnancy rates may differ when using the Trussel 1998 method to define average conception probability for particular study populations, a remarkable difference was observed between the estimation for the meta-analysis of Glasier and colleagues (2010)[8] and that of the WHO studies.

There are a many factors that can affect a woman's probability of pregnancy, i.e. the fertile window and ovulation. The expected day of ovulation is estimated as the usual cycle length minus 14 days. However, in only about 30% of women is the fertile window entirely between days 10 and 17, as identified by the clinical guidelines. The other 70% of women reach their fertile window earlier and others much later. The question is further complicated by women who have irregular cycles; their percentage was reported to be 16% in a study by Wilcox and colleagues (2001)[9] During the study, these women tended to ovulate later and at more variable times, resulting in their fertile days being spread more broadly across their cycles.

Despite its great practical importance, the number of fertile days during the menstrual cycle has been difficult to specify. Just as the day of ovulation varies from cycle to cycle, so does the timing of fertile days. A multicenter study by the WHO estimated that there are 10 presumably fertile days per cycle, on the basis of the characteristics of the cervical mucus. The length of the phase after the peak mucus day in the various centres parallels similar results obtained in the Colombo study. This multicentre study has produced a database of 7017 menstrual cycles contributed by 881 women. It provides improved knowledge on length and location of the "fertile window" (identified as of up to a 12-day duration) and the pattern and level of daily conception probability.

7 Trussel J et al.: New estimates of the effectiveness of the Yuzpe regimen of emergency contraception. Contraception (1998); 57: 363–69

8 Glasier A et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomized non-inferiority trial and meta-analysis. Lancet (2010); 375: 555–62.

9 Wilcox et al., The timing of the "fertile window" in the menstrual cycle: day specific estimates from a prospective study. BMJ, (2001) Mar 10;322(7286):617

Eight studies have been conducted with the regimens of 0.75 mg LNG pills (1.5 mg in two split doses taken 12 hours apart) as well as the 1.5 mg LNG taken once as emergency contraceptives that can be used in support of the efficacy of LNG. Two of these comparative studies have been conducted for the registration dossier of UPA, HRA2914-507 and HRA2914-513. Studies from Von Hertzen and colleagues (2002)[10] and Arowojolu and colleagues (2002)[11] showed that a single 1.5 mg LNG dose was more efficacious than the regimen of two tablets of 0.75 mg LNG, taken 12 hours apart. The pregnancy rates increased with delay in starting treatment and if further acts of unprotected sexual intercourse took place after treatment (Arowojolu et al., 2002).

Table 1. List of individual studies for levonorgestrel

Study Identifier	Treatments; Dosage Regimen	Study Design and Type of Control	Number of Subjects	Type of Report
Ho and Kwan, 1993[12]	- 2 x 0.75mg LNG, 12 hours apart, - Yuzpe regimen (EE 100 µg plus LNG 0.5 mg, repeated 12 h later), up to 2 days after unprotected intercourse	Double-blind, randomised, single centre trial in Hong Kong.	834 women were enrolled and randomized, of whom 424 were assigned the Yuzpe regimen and 410 the LNG regimen.	Published article
WHO/HRP Study (Von Hertzen et al., 1998)[13]	- 2x0.75mg LNG, 12 hours apart, - Yuzpe regimen (EE 100 µg plus LNG 0.5 mg, repeated 12 h later), up to 3 days after unprotected intercourse	Double-blind, randomised, multinational trial, in 21 cities of 14 countries.	1998 women were enrolled and randomized, of whom 997 were assigned the Yuzpe regimen and 1001 the LNG regimen.	Published article, analysed by MAH
Pivotal WHO/HRP Study (Von Hertzen et al., 2002) (Final study report, 2003)	- 2x0.75mg LNG (as single 1.5mg dose), - 2x0.75mg LNG, 12 hours apart, - 10mg of mifepristone up to 5 days after unprotected intercourse	Double-blind, randomised multicenter trial. 15 countries in Asia/Europe.	4136 women were enrolled in the trial. 1380 were assigned mifepristone, 1379 single-dose LNG, and 1377 two-dose LNG (2x0.75mg, 12 hours apart)	Full report, analysed by MAH

10 von Hertzen H et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. Lancet, 2002; 360: 1803-10

11 Arowojolu AO et al. Comparative evaluation of the effectiveness and safety of two regimens of levonorgestrel for emergency contraception in Nigerians, Contraception 2002; 66: 269-273

12 Ho PC and Kwan MS: A prospective randomized comparison of levonorgestrel with the Yuzpe regimen in post-coital contraception. Human Reproduction 1993, 8:389-92

13 von Hertzen H et al. Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. Lancet, 1998; 352: 428-33.

Arowojolu et al., 2002	- 2x0.75mg LNG(as single 1.5mg dose), Group B - 2x0.75mg LNG, 12 hours apart, Group A up to 3 days after unprotected intercourse	Randomised, controlled, double-blind, multicenter, trial in Nigeria.	The study consisted of 1160 women, with 560 women in group A and 600 in group B. Of the 1118 women analysed, 545 women were in group A and 573 women were in group B.	Published article
Ngai et al., 2005[14]	- 2x0.75 mg LNG, 12 hours apart - 2x0.75 mg LNG, 24 hours apart	In China.	1027 subjects in the group with LNG 12 hours apart, and 1044 subjects in the group with LNG 24 hours apart.	Published article
Creinin et al., 2006[15] Study report HRA2914-507	- single dose of 50 mg of UPA - 2x0.75mg LNG, 12 hours apart, up to 3 days after unprotected intercourse	Randomised, double-blind non-inferiority trial in seven sites in the USA.	1,672 women were enrolled and randomly assigned, 832 to UPA and 840 to LNG. Efficacy was evaluable in 775 of UPA users and 774 of LNG users.	Full report, analysed by MAH
Dada et al., 2010[16]	- 2x0.75mg LNG (as single 1.5mg dose), -2x0.75mg LNG, 12 hours apart, up to 5 days after unprotected intercourse	Randomised, controlled, double-blind, multicenter, non-inferiority trial in Nigeria.	A total of 3022 participants were enrolled in the trial. 2823 participants included in the efficacy analysis, 1414 in the single-dose group and 1409 in the 2x0.75mg group.	Published article, analysed by MAH
Glasier et al., 2010 Study report HRA2914-513	- single dose of 30 mg of UPA - single 1.5mg dose LNG up to 5 days after unprotected intercourse	Randomised, multicentre, single-blind, non-inferiority trial. 35 sites; UK (10), Ireland (1), US (24).	2221 women were randomly assigned to receive a single, supervised dose of 30 mg UPA (n=1104) or single 1.5 mg LNG (n=1117) orally.	Full report, analysed by MAH

In addition to these studies, two additional studies were conducted to support efficacy and safety for UPA. Those studies were HRA2914-508 and HRA2914-509.

14 Ngai SW et al.: A randomized trial to compare 24 h versus 12 h double dose regimen of levonorgestrel for emergency contraception. Human Reproduction (2005), 20:307-11

15 Creinin MD et al.: Progesterone receptor modulator for emergency contraception: a randomized controlled trial. Obstet Gynecol (2006);108:1089–97

16 Dada OA et al. A randomized, double-blind, non-inferiority study to compare two regimens of levonorgestrel for emergency contraception in Nigeria. Contraception (2010); 82: 373–378.

Table 2. List of additional studies for UPA

Study Identifier	Treatments; Dosage Regimen	Study Design and Type of Control	Number of Subjects	Type of Report
Study report HRA2914-508	- single dose of 10 mg micronised UPA - single dose of 50 mg unmicronised UPA up to 3 days after unprotected intercourse	Randomised, double-blind trial at nine study sites in the USA.	812 women were enrolled and randomly assigned, 399 to 10 mg UPA and 415 to 50 mg UPA.	Full study report, analysed by MAH
Study report HRA2914-509	- single dose of 30 mg micronised UPA Between 48 (2 days) and 120 hours (5 days) after unprotected intercourse	Multicentre, open label, single arm, non-inferiority trial.	1533 women received a single dose of 30 mg UPA orally.	Full study report, analysed by MAH

2.3.3. Efficacy for LNG

Eight studies have been conducted for LNG emergency contraceptives that can be used for the assessment of efficacy (see table above).

One of the MAHs performed a meta-analysis on three WHO studies (Von Hertzen et al., 1998 and 2002; Dada et al., 2010). This meta-analysis will be referred hereafter as the three WHO studies meta-analysis. For the other studies the MAH indicated that they did not have all the needed parameters to be included in the analysis.

Another MAH performed a meta-analysis on the two comparative studies HRA2914-507 (Creinin et al., 2006) and HRA2915-513 (Glasier et al., 2010) that were part of the registration dossier for UPA.

The data of the studies of Ho and Kwan (1993), Arowojolu (2002) and Ngai (2005) were not analysed in detail as they have been provided as published articles only.

Additionally, an open label tolerance study was part of the national registration dossier of emergency contraceptive containing LNG (Norlevo). This open label tolerance study was not considered pivotal for this assessment, as efficacy was not investigated in line with the other studies provided. As the primary goal of the study was safety, no strict procedures were followed in the assessment of efficacy. Pregnancy was not ruled out before treatment intake, and pregnancy testing at follow-up was not systemically performed. Additionally, possible further acts of unprotected intercourse were not reported.

2.3.3.1. Description of meta-analysis of the studies

The three WHO studies included in the meta-analysis comprise of 5859 women and 59 pregnancies.

These studies were conducted in Africa (2679 women, 46%), Asia (1925 women, 33%) and America/Australia/Europe (1255 women, 21%). The women included in the three WHO studies (Von Hertzen et al., 1998; Von Hertzen et al., 2002; Dada et al., 2010) only had one act of unprotected intercourse. Women with off-label use, i.e. use between 72 – 120 hours after unprotected intercourse were not included. The meta-analysis both included subjects with 2x0.75 mg LNG taken as a single dose, and 2x0.75 mg LNG taken 12 hours apart (see table 1, above). In the studies from Von Hertzen and colleagues (2002) and Dada and colleagues (2010) a comparable number of subjects was included in these two dose regimens. The study from Von Hertzen and colleagues (1998) only included the dose regimen 2x0.75 mg LNG taken 12 hours apart.

The initially submitted meta-analysis of two comparative studies on LNG of another MAH included 1731 women and 38 pregnancies. These studies were conducted in the USA, United Kingdom and Ireland. These two studies included in addition women who had multiple acts of unprotected intercourse (4.7% of the 1731 women). Furthermore women who used LNG off-label, i.e. use between 72 – 120 hours after unprotected intercourse (UPI), were also included. This comprised 106 subjects (and 3 pregnancies that occurred in these women). Similarly this meta-analysis includes subjects that had taken 2x0.75 mg LNG taken 12 hours apart in study HRA2914-507 and 2x0.75 mg LNG as a single dose in study HRA2914-513.

Lastly, the two study populations included in this meta-analysis are slightly different. The primary efficacy population in study HRA2914-507 (Creinin et al., 2006) was the Efficacy Evaluable population consisting of all subjects who took both doses of the study drug without additional emergency contraceptive treatment during the study cycle and met one of the post-treatment criteria (i.e. had menses with a negative urine pregnancy test; verified amenorrheic with a negative pregnancy test; or verified as a post-treatment pregnancy).

In study HRA2914-513 (Glasier et al., 2010) the primary efficacy population was the mITT population defined as randomised and received study drug; had at least one UPI in the current cycle before enrolment; participated for the first time in the current study; known pregnancy status using high sensitivity urinary pregnancy test after emergency contraceptive intake; 35 years of age or younger; if pregnant, pregnancy not identified as started before emergency contraceptive intake or as “not compatible” with an emergency contraceptive failure, based on independent evaluation as assessed by the Data and Safety Monitoring Board.

After performing a new analysis excluding off-label use (i.e. intake between 72-120 hours after UPI) and those women who had had further acts of unprotected intercourse, this new meta-analysis based on the two comparative studies on LNG included 1548 subjects and 29 pregnancies.

2.3.3.2. Body weight and pregnancy rate

Meta-analysis of three WHO studies:

In the meta-analysis based on three WHO studies (Von Hertzen et al., 1998; Von Hertzen et al., 2002; Dada et al., 2010), the pregnancy rate in women with a weight between 75-79 kg and above 80 kg was slightly lower than in women with a weight of 74 kg or lower. However, a limited number of subjects was included in the weight groups ‘75-79 kg’ and ‘above 80 kg’.

Table 3. Number and frequency of pregnancies by weight classes, the three WHO trials

Table of Pregnancies by weight class				
Pregnant	**weight class (kg)**			
N	**0 - 74**	**75 - 79**	**>80**	**Total**
NO	5299	240	261	5800
YES (Column %)	57 (1.06%)	1 (0.41%)	1 (0.38%)	59 (1.01%)
Total	5356	241	262	5859

Meta-analysis of two comparative studies:

In contrast, the other meta-analysis suggests a trend for an increased pregnancy rate in the two highest weight categories selected, i.e. '75-85 kg' and '≥ 85 kg'. Especially, in these two highest weight categories, the confidence limits are very wide, due to the low number of subjects included in these categories.

Table 4. Pregnancy rate (95% CI exact Clopper-Pearson method) according to weight categories (women treated by LNG, studies HRA2914-507 and HRA2914-513 combined)

Weight	< 55 kg	[55-65[kg	[65-75[kg	[75-85[kg	≥ 85 kg
N, PEP	**349**	**608**	**426**	**155**	**193**
N pregnancies (Pregnancy rate)	3 (0.9%)	8 (1.30%)	6 (1.4%)	10 (6.4%)	11 (5.7%)
Exact Clopper-Pearson 95% CI	(0.18; 2.49)	(0.57; 2.58)	(0.52; 3.04)	(3.14; 11.54)	(2.88; 9.97)
N, PEP excluding EC intake beyond 72h	**322**	**578**	**404**	**144**	**176**
N pregnancies (Pregnancy rate)	3 (0.93%)	8 (1.38%)	5 (1.24%)	9 (6.25%)	10 (5.68%)
Exact Clopper-Pearson 95% CI	(0.19; 2.70)	(0.60; 2.71)	(0.40; 2.86)	(2.90; 11.53)	(2.76; 10.20)
N, PEP excluding EC intake beyond 72h and further intercourse	**306**	**550**	**388**	**138**	**166**
N pregnancies (Pregnancy rate)	2 (0.65%)	7 (1.27%)	5 (1.29%)	6 (4.35%)	9 (5.42%)
Exact Clopper-Pearson 95% CI	(0.08; 2.34)	(0.51; 2.60)	(0.42; 2.98)	(1.61; 9.22)	(2.51; 10.04)

PEP : primary efficacy population

The number of subjects with body weight above 80 kg included in both meta-analyses is comparable, i.e. 261 subjects in the first analysis and 257 subjects in the second analysis. However, the pregnancy rates for women above 80 kg are completely different with an estimated pregnancy rate of 0.41% (75-79 kg) and 0.38% (above 80 kg) in the first analysis (see table 3) versus 4.35% (75-85 kg) and 5.42% (≥ 85 kg) in the analysis (see table 4), which excluded off-label use.

2.3.3.3. BMI and pregnancy rate

Meta-analysis of three WHO studies:

Crude rates of pregnancy, excluding off-label use (i.e. intake between 72-120 hours and/or further UPI), were calculated for the meta-analysis based on the three WHO studies.

Table 5. Number and frequency of pregnancies by BMI classes, in the three WHO trials (excluding off-label use).

BMI (kg/m2)	**Underweight 0 - 18.5**	**Normal 18.5-25**	**Overweight 25-30**	**Obese 30-**
N total	600	3952	1051	256
N pregnancies	11	39	6	3
Pregnancy rate	1.83%	0.99%	0.57%	1.17%
Confidence Interval (Fisher exact 95% CI)	0.92 – 3.26	0.70 – 1.35	0.21 – 1.24	0.24 – 3.39

The analysis for women with treatment delay of ≤ 120 hours showed that the pregnancy rates for the individual WHO categories are similar compared to the analysis on population for women with treatment delay of ≤ 72 hours for the categories underweight 1.83% for PP (0-72) versus 1.96% for ITT (0-120), normal 0.99% for PP (0-72) versus 1.05% for ITT (0-120), and overweight 0.57% for PP (0-72) versus 0.62% for ITT (0-120). For the category obese, however, the pregnancy rate in the ITT population (0-120) is higher than for the PP population (0-72), i.e. 1.17% for PP (0-72) versus 2.08% for ITT (0-120). This is due to the fact that the difference between both analyses is three pregnancies, 6 in the ITT (0-120) population versus 3 in the PP (0-72) population in the obese category. Nevertheless, the pregnancy rate of 2.08% is comparable to the pregnancy rate of the underweight category of 1.96%. Further, the confidence intervals in the obese category are very wide and overlapping other categories, because only 282 subjects were included with a BMI of 30 or higher.

Meta-analysis of two comparative studies

Crude rates of pregnancy, including and excluding off-label use, were also calculated for the second meta-analysis including the two comparative studies.

Table 6. Number and frequency of pregnancies by BMI classes in studies of Creinin et al., 2006 and Glasier et al., 2010 (excluding off-label use)

BMI (kg/m^2)	Underweight 0 - 18.5	Normal 18.5-25	Overweight 25-30	Obese ≥ 30
N total	64	933	339	212
N pregnancies	1	9	8	11
Pregnancy rate	1.56%	0.96%	2.36%	5.19%
95% Confidence Interval	0.04 – 8.40	0.44 – 1.82	1.02 – 4.60	2.62 – 9.09

Comparing results of both meta-analyses, it appeared that although the pregnancy rates in normal/underweight women are comparable in both datasets, which excluded off-label use beyond 72 hours, the pregnancy rates between the two meta-analyses are in contrast with each other for the BMI classes 'overweight (BMI 25-30 kg/m^2)' and 'obese (BMI > 30 kg/m^2)'. In the first analysis in 'overweight women' the pregnancy rate was only 0.57%, whereas this was 2.36% in the second dataset that included off-label use. The largest difference was observed in the 'obese' category (BMI above 30), which has a similar pregnancy rate as the normal/underweight category, but is much higher (5.19%) in the second analysis. There is a trend for a BMI-dependent decrease of contraceptive efficacy, as the pregnancy rate increases. Although the confidence limits were wide of the obese group (BMI>30), due to the limited number of subjects included in this category, the confidence limits of the obese category (CI 2.62 -9.09) do not overlap with the normal weight category (BMI 18.5-25; CI 0.44 – 1.82).

As already mentioned above both meta-analyses excluded off-label use of LNG, i.e. intake later than 72 hours after unprotected intercourse and women who had further acts of unprotected intercourse.

2.3.3.4. Confounding factors

As expected, the effect of conception probability (based on the method of Trussel; 1999)[17], was a significant variable for the risk of pregnancy.

Meta-analysis of three WHO studies:

The most significant variable was the *geographical location by continents* (p<0.001), showing an increased risk of pregnancy in subjects from Asia compared to those from the rest of the world; a reduced risk was seen in subjects from Nigeria compared to the same worldwide group. A possible explanation could be the higher conception probability that may be found among Chinese women, which was observed in published comparative studies (Bilian et al., 2010)[18].

Table 7. Pregnancies by 'continents' and countries, three WHO trials[19]

	Africa (Nigeria)
Total	2679
Not pregnant	2665
Pregnant	14
Pregnant %	**0.52**

	China	Hong Kong	India	Mongolia	**Asia**
Total	1401	159	119	246	1925
Not pregnant	1374	157	117	244	1892
Pregnant	27	2	2	2	33
Pregnant %	1.93	1.26	1.68	0.81	**1.71**

	AUS	CAN	FIN	GEO	HUN	NZL	PAN	SVN	SWE	SWZ	GBR	USA	**Am/Aus/Eur**
Total	39	31	73	141	224	89	28	126	208	171	92	33	1255

17 Trussel J: Updated estimates of the effectiveness of the Yuzpe regimen of emergency contraception. Contraception 1999;59:147–151

18 Bilian X et al.: Conception probabilities at different days of menstrual cycle in Chinese women. Fertility and Sterility_ Vol. 94, No. 4, September 2010

19 Alpha-3 country codes are presented according to ISO 3166 standard.

Not pregnant	38	31	72	141	224	87	28	123	20	168	92	33	1057
Pregnant	1	0	1	0	0	2	0	3	2	3	0	0	12
Pregnant %	2.56	0.00	1.37	0.00	0.00	2.25	0.00	2.38	0.96	1.75	0.00	0.00	**0.96**

Moreover, the analysis showed that 3 out of the 6 women who became pregnant in the obese category had taken LNG off-label in the Dada and colleagues study (2010). These 3 pregnancies have a large effect on the crude pregnancy rate in the obese category, which is 2.6% when off-label use is included (6 out of 230 subjects). The exact pregnancy rate excluding off-label use and further acts of UPI in the obese category in the Dada (2010) study remains unknown, as it is unknown what the number of subjects is in the Dada (2010) study that took LNG off-label and/or had further acts of UPI in the obese category.

The division in BMI categories in the Dada and colleagues study (2010) shows a higher pregnancy rate only in the BMI category above 30. However, the number of obese subjects is small, which makes the point estimate not robust, considering the wide confidence intervals. The pregnancy rates for the underweight/normal weight and overweight categories are considered very low, 0.34% and 0.63%, respectively. Further, the division into body weight categories (<75 kg, 75-80 kg, >80 kg) are also very low. All categories are below 1%.

In addition, in the Nigerian Dada and colleagues (2010) study a special subgroup of subjects was evident on the body weight vs. body height scatter plot: the apparent physiological peculiarity of these subjects is that they are exceptionally short (below 1.45 m) for their weight. A relatively large percentage of pregnancies occurred in short subjects (below 1.45 m) with a high BMI.

Further, an effect was seen of age (i.e. probability of pregnancy initially increased, peaked at around 30 years and then declined) and treatment delay (i.e. up to 48 hours treatment delay was not observed to influence the chances of pregnancy, but this changed after that). Especially, the effect of treatment delay supported that women should take emergency contraception as soon as possible after having had unprotected sexual intercourse.

Meta-analysis of two comparative studies:

The effect of the confounding factors of ‘further acts of UPI’, ‘age’, ‘ethnic group, ‘time to drug intake’ and ‘country (EU/USA)’ on the pregnancy risk showed that there is no statistically significant difference between the different weight groups in further UPI. Also, there was no relationship between weight and further UPI. Further, the possible confounding factors ‘age’, ‘ethnic group’, ‘time to drug intake’ and ‘country (EU/USA)’ were investigated. The analyses suggested that these factors did not lead to a significant contribution to the pregnancy risk. These values were not significant for BMI or for weight.

Comparing the results on confounding reported in both meta-analyses, the overall the impact of confounding factors (i.e. age, ethnicity, delay between UPI and treatment intake) that might explain discrepancy of results between both meta-analysis could not be excluded.

2.3.3.5. Spontaneous reporting

The MAHs have analysed their own large safety database, as well as the WHO VigiBase for cases of Loss of Efficacy. As spontaneously reported data have limitations, the data can only be used as supportive data. The data do not show a signal that with increased body weight efficacy decreases. However, these data should be interpreted cautiously since the extent of usage may differ across weight categories. In addition, there are several other unknown factors (e.g. conception probability, further acts of intercourse, etc.). Thus, even if the data do not indicate a high representation of

overweight or obese females reporting loss of efficacy, the data from spontaneous reporting are deemed to be of limited value in this assessment.

2.3.4. Efficacy for UPA

The MAH for UPA presented several analyses on the four studies conducted with ellaOne that are present in the registration dossier. Taking all four studies together (Table 8), the total number of pregnancies included was 53 in the UPA arms (NB: 30 mg micronised UPA is bioequivalent to 50 mg unmicronised UPA). In this table women with further acts of unprotected intercourse are still included.

Table 8. Studies conducted for UPA

Study	Time elapsed since UPI	Treatment	Observed pregnancies	Pregnancy rate (95% CI)
HRA2914-**507** Non-inferiority study	0-72h	50mg unmicronised UPA (n=773)	7	0.91 (0.37, 1.86)
		1.5mg LNG (n=773)	13	0.68 (0.90, 2.86)
HRA2914-**508** Non-inferiority study	0-72h	10mg micronised UPA (n=365)	10	2.74 (0.32, 4.99)
		50mg unmicronised UPA (n=384)	5	1.30 (0.42, 3.02)
HRA2914-**509** Uncontrolled study vs no use	48-120h	30mg micronized UPA (n=1241)	26	2.10 (1.41, 3.10)
HRA2914-**513** Non-inferiority study	0-120h	30mg micronized UPA (n=941)	15	1.60 (0.93, 2.67)
		1.5mg LNG (n=958)	25	2.62 (1.75, 3.89)

2.3.4.1. Body weight and pregnancy rate

The pregnancy rates according to weight categories were separately presented for the three controlled studies (Table 9) and one open label study (Table 10). The data show that there seems to be a non-significant trend for a higher pregnancy rate in the highest weight category, although the confidence limits are wide.

Table 9. Pregnancy rate (95%CI exact Clopper-Pearson method) according to weight categories (women treated by UPA, randomised studies HRA2914-507, HRA2914-513 and HRA2914-508 combined)

Weight categories (kg)	**< 55 kg (n=425)**	**[55-65[kg (n=733)**	**[65-75[kg (n=480)**	**[75-85[kg (n=212)**	**≥ 85 kg (n=248)**
N	3	10	5	3	6
Pregnancy rate (%)	0.71%	1.36%	1.04%	1.42%	2.42%
95% CI	[0.15 – **2.04**]	[0.65 - **2.49**]	[0.34 - **2.41**]	[0.29 - *4.08*]	[0.89 – *5.19*]

Table 10. Pregnancy rate (95%CI exact Clopper-Pearson method) according to weight categories (women treated by UPA, open label study HRA2914-509)

Weight Categories (kg)	**< 55 kg (n=260)**	**[55-65[kg (n=410)**	**[65-75[kg (n=260)**	**[75-85[kg (n=140)**	**≥ 85 kg (n=169)**
N	5	10	3	3	5
Pregnancy rate (%)	1.9%	2.4%	1.1%	2.1%	3.0%
95% CI	[0.6 - *4.4*]	[1.2 - *4.4*]	[0.2 - **3.3**]	[0.4 - *6.1*]	[1.0 - *6.8*]

2.3.4.2. BMI and pregnancy rate

The pregnancy rates according to BMI categories were also separately presented for the three controlled studies and one open label study, as well as for all four studies combined.

The data for the three controlled trials show that in the highest BMI category (BMI> 35) the pregnancy rate was the highest (3.54%), though the number of women in this category is low, and consequently confidence limits are wide (095% CI ;0.97-8.81). In the uncontrolled study the highest BMI category (BMI> 35) did not correspond to the highest pregnancy rate (2.30% for BMI>35, 3.70% for BMI 30-35, 2.26% for BMI 25-30).

The post-hoc subgroup analysis including all four studies (table 11) still shows that there might be a trend, although this trend is weaker than for the post-hoc subgroup analysis including only the three studies. The pregnancy rate in the highest BMI category (BMI> 30) was 2.57% while for the BMI 25-30 category the pregnancy rate was 1.29%. In this analysis women with further acts of unprotected intercourse were excluded.

Table 11. Meta-analysis on four clinical studies conducted with UPA

BMI (kg/m²)	Underweight 0 - 18.5	Normal 18.5-25	Overweight 25-30	Obese 30-
N total	128	1866	699	467
N pregnancies	0	23	9	12
Pregnancy rate	0.00%	1.23%	1.29%	2.57%
95% Confidence Interval	0.00 – 2.84	0.78 – 1.84	0.59 – 2.43	1.34 - 4.45

It can be concluded that the analyses for BMI with all four studies on UPA combined, suggest a trend for a higher pregnancy rate in the highest body weight category (≥ 95 kg) and BMI category (BMI ≥30).

2.3.4.3. Confounding factors

Analyses were conducted to assess time-to-intake, ethnic group (white, Asian, black, other) as well as age (that can impact fertility) and country (EU/USA were the two main geographic regions) as possible confounders for the effect of weight/BMI on pregnancy risk in addition to further UPI and conception probability. The analysis was conducted on the primary efficacy population and also after excluding occurrence of further UPI. These analyses were conducted on all four studies (N=3337 and 53 pregnancies). The analyses suggested that these factors did not lead to a significant contribution to the pregnancy risk.

2.3.5. Discussion

Emergency contraceptives can be used to prevent an unintended pregnancy following an unprotected sexual intercourse or in case of failure of a contraceptive method. The emergency contraceptives can be divided into levonorgestrel (LNG)- and UPA-containing emergency contraceptives and they act by inhibiting and/or delaying ovulation.

The use of emergency contraception is an occasional method that is far less effective compared with most contraceptive products used on a regular basis, e.g. combined hormonal contraceptives, gestagen-only pills and various long-acting methods like intra-uterine devices and implants.

The CHMP reviewed all data from clinical studies, published literature, post-marketing experience, including responses submitted by the marketing authorisation holders (MAHs), on the efficacy of emergency contraceptive medicinal products containing LNG or UPA, in particular with regards to the relation of high weight/BMI of women.

Levonorgestrel (LNG)

There are limited and inconclusive data from clinical trials that evaluated the effect of high body weight/high BMI on the contraceptive efficacy. In the meta-analysis including the three WHO studies, primarily including African and Asian women, no trend for a reduced efficacy with increasing body weight/BMI was observed (Table 5 above). In contrast, in the two studies of Creinin and colleagues

(2006) and Glasier and colleagues (2010), primarily including Caucasian women, reduced contraceptive efficacy was observed with increasing body weight or BMI (Table 6).

Both meta-analyses excluded intake later than 72 hours after unprotected intercourse (i.e. off-label use of LNG) and women who had further acts of unprotected intercourse.

The data are currently too limited and therefore insufficiently precise to draw definite conclusions whether efficacy is negatively influenced by increased body weight and BMI; for instance for the obese category (BMI ≥30) three pregnancies were reported in the first analysis, and eleven pregnancies in the second. It is unknown what the explanation is for the contradicting results in both meta-analyses. All together, the current data are considered not robust enough to support the current recommendation of decreased efficacy in women with body weight above 75 kg and inefficacy in women with body weight above 80 kg as is currently included in the product information of one LNG-containing emergency contraceptive medicinal product (Norlevo).

A range of different factors have an impact on a woman´s fertility and the ability of emergency contraceptives to prevent a pregnancy, e.g. timing of intake of emergency contraception in relation to intercourse, conception probability, further acts of unprotected intercourse, age, ethnicity, previous infections of the genital tract, fertility, male fertility, etc. This is reflected in the wide range of estimates of prevented fraction across different studies. Therefore, even if data from some studies suggest a lower ability of LNG-containing emergency contraceptives to prevent pregnancies in women of higher weight/BMI, this is only one factor influencing the effect and it is difficult to define a certain cut-off for weight/BMI at which no effect is present.

The safety profile of LNG-containing emergency contraceptives remains favourable as this referral did not discuss any safety issues.

Overall for LNG-containing emergency contraceptives it is concluded that there is limited and inconclusive data on the effect of high body weight/high BMI on the contraceptive efficacy.

The CHMP proposed that a warning in section 4.4 of the SmPC is appropriate to indicate that limited and inconclusive data are present regarding a possible reduced efficacy in women with a high body weight/BMI. Further, the data of the two meta-analyses should be presented in section 5.1 of the SmPC. This information should also be reflected in the package leaflet. Further, since the limited data available do not support with any certainty the conclusion that their contraceptive effect is reduced in women with high body weight, no adjustment of the dose is recommended, and any information that is already included in section 4.2 of the SmPC making reference to effect and body weight should be removed. The safety profile of LNG-containing emergency contraceptives remains favourable.

The CHMP is of the opinion that further data is needed especially of pharmacodynamic/pharmacokinetic (PD/PK) nature in order to provide more information on the issue of high body weight/BMI and ovulation inhibition. Such study may have limitation especially in the clinical interpretation of the results. However, considering the large impact of any proof of decreased efficacy in obese women, it is strongly recommended to investigate the pharmacodynamic effect (ovulation inhibition) of LNG in obese women.

Ulipristal acetate (UPA)

The data used in the analyses of effect of UPA in relation to weight/BMI are partly based on the same studies two studies for LNG (as above), and another randomised controlled study (HRA2914-507, HRA2914-508, HRA2914-513) as well as an open label study (HRA2914-509). Similar analyses were performed. A trend was observed in the UPA group for increasing number of pregnancies with increasing weight or BMI, although not as strong as for LNG-containing emergency contraceptives.

However, the analyses are based on a limited number of women, especially in the highest body weight/BMI categories, which subsequently result in very wide and overlapping 95% confidence limits.

While the analyses of data from the three randomised controlled trials in which 2,098 women received UPA indicate a weak effect of body weight or BMI on pregnancy rates, the open label study (n=1,241) indicated no such effect. From these data there is no clear indication of an effect of weight or BMI on efficacy in general, or specifically among overweight or obese women.

The data are currently too limited and therefore insufficiently precise to draw definite conclusions whether efficacy is negatively influenced by increased body weight and BMI (see Table 11 above).

However, the CHMP proposed that a warning is included in section 4.4 of the SmPC is appropriate to indicate that limited and inconclusive data are present regarding a possible reduced efficacy in women with a high body weight/BMI. Further, in all women emergency contraception should be taken as soon as possible after unprotected intercourse. Further, the data of the meta-analysis should be presented in section 5.1 of the SmPC.

The safety profile of UPA-containing emergency contraceptives remains favourable as this referral did not discuss any safety issues.

Conducting a pharmacodynamic/pharmacokinetic (PD/PK) study may provide more information on the issue of high body weight/BMI and ovulation inhibition. It is agreed that such a PD/PK study has limitations as the translation to clinical treatment recommendations may be difficult due to the high variability between women. However, considering the large impact of any proof of decreased efficacy in obese women, it is strongly recommended to investigate the pharmacodynamic effect (ovulation inhibition) of UPA in obese women, in the future.

Conclusions

For LNG-containing emergency contraceptives overall it is concluded that there is limited and inconsistent data on the effect of high body weight/high BMI on the contraceptive efficacy. In the three WHO studies (Von Hertzen et al., 1998 and 2002; Dada et al., 2010) no trend for a reduced efficacy with increasing body weight/BMI was observed, whereas in the two other studies (Creinin et al., 2006 and Glasier et al., 2010) a reduced contraceptive efficacy was observed with increasing body weight or BMI. Both meta-analyses excluded off-label use of LNG-containing of emergency contraceptives, i.e. intake later than 72 hours after unprotected intercourse and women who had further acts of unprotected intercourse.

For UPA-containing emergency contraceptive products (ellaOne) it is concluded that limited and inconclusive data suggest that there may be reduced efficacy of UPA with increased body weight in women. Further, in all women emergency contraception should be taken as soon as possible after unprotected intercourse.

The CHMP also agreed that a further PK/PD study needs to be conducted for LNG- and UPA-containing emergency contraceptive medicinal products to provide more information on the issue of high body weight/BMI and ovulation inhibition. The CHMP recommended that the pharmacodynamic effect (ovulation inhibition) in obese women is investigated in the future.

2.4. Overall benefit/risk assessment

The Committee concluded that the benefit-risk balance of emergency contraceptive medicinal products containing LNG or UPA remains positive, subject to the warnings and changes to the product information agreed.

2.5. Communication plan

The CHMP agreed that for LNG-containing emergency contraceptives only, and in view of the public interest on the issue assessed the national competent authorities of the MSs may decide to communicate on the outcome of this review at national level, owing to the differences in each national system and the legal status of each product (LNG is a prescription medicine in some MSs or distributed over-the-counter (OTC) in others).

Routine communication to the public will be followed for ellaOne (UPA).

2.6. Changes to the product information

2.6.1. Levonorgestrel

A. Summary of product characteristics

Section 4.2 Posology and methods of administration

Any reference to weight and efficacy should be removed from this section as the data are inconsistent and inconclusive.

Section 4.4 Special warnings and precautions for use

A warning in this section of the SmPC is considered appropriate to indicate that inconclusive data are present regarding a possible reduced efficacy in women with a high body weight/BMI.

Section 5.1 Pharmacodynamic properties

The data of the two meta-analyses should be presented in this section of the SmPC.

B. Package leaflet

The package leaflet has been updated accordingly to include the information of the effect of weight/BMI to the efficacy of the products.

2.6.2. Ulipristal acetate

A. Summary of product characteristics

Section 4.4 Special warnings and precautions for use

A warning in this section of the SmPC is considered appropriate to indicate that inconclusive data are present regarding a possible reduced efficacy in women with a high body weight/BMI.

Section 5.1 Pharmacodynamic properties

The data of the analysis should be presented in this section of the SmPC.

B. Package leaflet

The package leaflet has been updated accordingly to include the information of the effect of weight/BMI to the efficacy of the products.

3. Overall conclusion

Having considered the overall submitted data provided by the MAHs in writing the CHMP concluded that the benefit-risk balance of emergency contraceptive medicinal products containing LNG or UPA remains positive for all women regardless of body weight/BMI, subject to the warnings and changes to the product information agreed.

Therefore, the CHMP recommended the variation to the terms of the marketing authorisation for the emergency contraceptive medicinal products containing LNG or UPA, for which the relevant sections of the summary of product characteristics, package leaflet are set out in the CHMP opinion.

Grounds for the variation to the terms of the marketing authorisation

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC for the emergency contraceptive medicinal products containing LNG or UPA.
- The Committee reviewed all data from clinical studies, published literature, post-marketing experience, including responses submitted by the marketing authorisation holders (MAHs), on the efficacy of emergency contraceptive medicinal products containing LNG or UPA, in particular with regards to a possible effect of high weight/BMI of women.
- The CHMP concluded that the available data is limited and does not support a definite conclusion that increased bodyweight reduces efficacy of emergency contraceptives medicinal products containing LNG or UPA. Available data should be included in the product information, but no restrictions of use based on body weight/BMI are recommended.
- The Committee considered that in view of the currently available data, the benefit-risk balance of emergency contraceptive medicinal products containing LNG or UPA is favourable, subject to warnings and other changes to the product information. In particular, the information that limited, but inconclusive data suggest that there may be reduced efficacy of these medicinal products with increased body weight in women.

The Committee, as a consequence, concluded that the benefit-risk balance of emergency contraceptive medicinal products containing LNG or UPA remains positive, subject to the warnings and changes to the product information agreed.