Annex II

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

Scientific conclusions

Overall summary of the scientific evaluation of emergency contraceptives medicinal products containing levonorgestrel or ulipristal acetate

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 ulipristal acetate (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.

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asking the CHMP to give its opinion on whether the marketing authorisations should be maintained, varied, suspended or withdrawn. The CHMP was requested to assess whether the efficacy of emergency contraceptives is affected in relation to body weight and/or body mass index (BMI) of the women.

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)

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.

Eight relevant studies with LNG-containing emergency contraceptives are available in public literature.

During the data submission an analysis was provided on three WHO studies (Von Hertzen et al., 1998 [1] and 2002 [2]; Dada et al., 2010 [3]) as well as an analysis on two other studies (Creinin et al., 2006 [4]; Glasier et al., 2010 [5]).

The rest of the studies have been submitted in the form of published literature.

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 1). In contrast, in the two comparative studies of Creinin and colleagues (2006) and Glasier and colleagues (2010), primarily including Caucasian women, a reduced contraceptive efficacy was observed with increasing body weight or BMI (Table 2). Both meta-analyses

1 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.

2 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

3 Dada OA *et al.* A randomized, double-blind, noninferiority study to compare two regimens of levonorgestrel for emergency contraception in Nigeria. *Contraception* 2010; 82: 373–378.

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

5 Glasier A *et al.* Ulipristal acetate versus levonorgestrel for emergency contraception: a randomized noninferiority trial and meta-analysis. *Lancet* 2010; 375: 555–62.

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.

Table 1: Meta-analysis on three WHO studies (Von Hertzen et al., 1998 and 2002; Dada et al., 2010)

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	0.92 – 3.26	0.70 – 1.35	0.21 – 1.24	0.24 – 3.39

Table 2: Meta-analysis on studies of Creinin et al., 2006 and Glasier et al., 2010

BMI (kg/m2)	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%
Confidence Interval	0.04 – 8.40	0.44 – 1.82	1.02 – 4.60	2.62 – 9.09

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, 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.

Overall for of LNG-containing emergency contraceptives it is concluded that there is limited 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 summary of product characteristics (SmPC) is an appropriate routine risk minimisation measure to reflect 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 reflected 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 bodyweight, no adjustment of the dose is recommended at this stage, and any information that already is included in the section 4.2 of the SmPC making reference to effect and body weight should be removed.

Ulipristal acetate (UPA)

Ulipristal acetate (UPA) (30 mg) (ellaOne) is an orally 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 in 73 countries worldwide and it is being marketed for five years.

The data used in the analyses of effect of UPA in relation to weight/BMI are partly based on the same studies two abovementioned studies for LNG, 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. 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.

Table 3: Meta-analysis on four clinical studies conducted with UPA

BMI (kg/m^2)	**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

The CHMP concluded 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 and that in all women emergency contraception should be taken as soon as possible after unprotected intercourse, regardless of the woman's body weight or BMI. Further, the data of the meta-analysis should be presented in section 5.1 of the SmPC.

The information in the SmPC should also be reflected in the package leaflet.

In addition the CHMP is of the opinion that conducting a pharmacodynamic/pharmacokinetic (PD/PK) study may provide some information which may help to further characterise the risk of decreased efficacy in women with high body weight/BMI and ovulation inhibition. Considering the need to further characterise this risk, the MAHs are strongly recommended to investigate the pharmacodynamic effect (ovulation inhibition) of LNG in obese women in the future.

Overall conclusion

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.

Benefit –risk balance

The Committee 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.

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 at this stage.
- 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, 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.