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Levonorgestrel and ulipristal remain suitable emergency contraceptives for all women, regardless of bodyweight

On 24 July 2014, the European Medicines Agency concluded its review of emergency contraceptives containing levonorgestrel or ulipristal acetate to assess whether increased bodyweight affects the effectiveness of these medicines in preventing unintended pregnancy following unprotected sexual intercourse or contraceptive failure. The Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that these emergency contraceptives could continue to be used in women of all weights as the benefits were considered to outweigh the risks.

In November 2013, following a national procedure, the product information of one emergency contraceptive containing levonorgestrel, Norlevo, was updated on the basis of results from two clinical studies to state that Norlevo is less effective in women weighing 75 kg or more and not effective in women weighing more than 80 kg. An EU-wide review was then started to assess whether similar information should be included in the product information for other emergency contraceptives that contain levonorgestrel, and for ellaOne, an emergency contraceptive that contains ulipristal acetate.

Having assessed all the available evidence on the effectiveness of emergency contraceptives, the CHMP considered that the data available are too limited and not robust enough to conclude with certainty that contraceptive effect is reduced with increased bodyweight, as stated in the product information for Norlevo. For levonorgestrel-containing products, some clinical studies have suggested a reduced effectiveness in women with high bodyweight, but in others no trend for a reduced effect with increasing bodyweight was observed. Similarly, for ulipristal acetate, although limited data from clinical trials suggest a possible trend for a reduced contraceptive effect, the data are too limited and insufficiently precise to draw definite conclusions. The CHMP recommended that the results of these studies should be included in the product information of emergency contraceptives, but that the statements on the impact of bodyweight in the product information for Norlevo should be deleted.

The CHMP considered that, with side effects generally mild, the safety profile of emergency contraceptives is favourable and they can continue to be taken regardless of the woman's bodyweight. Women should be reminded that emergency contraceptives should be taken as soon as possible following unprotected sexual intercourse. They should only be used as an occasional 'rescue' method as they do not work as well as regular contraceptive methods.

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The CHMP recommendation was sent to the European Commission, which issued a legally binding decision valid throughout the EU on 30 September 2014.

Information for women

- Emergency contraceptives are used to prevent unintended pregnancy following unprotected sexual intercourse or contraceptive failure.
- An EU-wide review was carried out to assess whether emergency contraceptives are less effective in overweight or obese women. It concluded that the limited data available do not support with certainty the previous conclusion that their contraceptive effect is reduced in women with high bodyweight.
- Emergency contraceptives can continue to be taken after unprotected intercourse or contraceptive failure, regardless of the woman's bodyweight. However, in order to maximise the likelihood that they will work, it is important that they are taken as soon as possible after unprotected intercourse.
- Women are reminded that emergency contraception is an occasional 'rescue' method, which does not work as well as regular methods of contraception, such as the pill.
- Women who have any questions or concerns should speak to their doctor or pharmacist.

Information to healthcare professionals

- Emergency contraceptives can continue to be used to prevent unintended pregnancy in women of any weight or body mass index (BMI). The available data are limited and not robust enough to support with certainty the previous conclusion of decreased contraceptive effect with increased bodyweight/BMI.
- Healthcare professionals should continue to remind women that emergency contraception is an occasional 'rescue' method and should not replace a regular contraceptive method.

For emergency contraceptives containing levonorgestrel, the Agency considered the following data:

- a meta-analysis of two published studies[1,2], which primarily included Caucasian women, where a reduced contraceptive efficacy was observed with increased bodyweight or BMI (pregnancy rate was 0.96% [CI: 0.44-1.82] in women with BMI 18.5-25; 2.36% [CI: 1.02-4.60] in women with BMI 25-30; and 5.19% [CI: 2.62-9.09] in women with BMI ≥30).
- a meta-analysis of three WHO studies[3,4,5], which primarily included African and Asian women. The results of this analysis conflict with the results above and show no trend for a reduced efficacy with increasing bodyweight/BMI (pregnancy rate was 0.99% [CI: 0.70-1.35] in women with BMI 18.5-25; 0.57% [CI: 0.21-1.24] in women with BMI 25-30; and 1.17% [CI: 0.24-3.39] in women with BMI ≥30).

Both meta-analyses did not include off-label use (i.e. intake later than 72 hours after unprotected sexual intercourse).

For ulipristal acetate, the Agency considered the following data:

- a meta-analysis of four clinical studies that were submitted as part of the application for marketing authorisation of ellaOne[6], which suggests a possible trend for a reduced contraceptive efficacy with high bodyweight or BMI, although confidence limits overlap (pregnancy rate was 1.23% [CI: 0.78-

1.84] in women with BMI 18.5-25; 1.29% [CI: 0.59-2.43] in women with BMI 25-30; and 2.57% [CI: 1.34-4.45] in women with BMI ≥30).

References.

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

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

3. 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.

4. 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.

5. 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.

6. Studies HRA2914-507, HRA2914-508, HRA2914-509 and HRA2914-513. For more information on these studies, see the CHMP assessment report for ellaOne: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001027/WC500023673.pdf

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More about the medicines

Emergency contraceptives are contraceptives used to prevent unintended pregnancy following unprotected sexual intercourse or contraceptive failure. The emergency contraceptives included in this review are medicines containing levonorgestrel, such as Norlevo, Levonelle/Postinor and Levodonna, which have been authorised in the EU through national procedures. The review also included a centrally-authorised medicine, ellaOne, which contains ulipristal acetate and was granted a marketing authorisation in the EU in 2009.

Emergency contraceptives work by stopping or delaying ovulation. Those containing levonorgestrel can be used up to 72 hours after unprotected sexual intercourse or contraceptive failure, while ulipristal acetate can be used up to 120 hours.

Levonorgestrel-containing emergency contraceptives are available 'over the counter' in several European countries. EllaOne can only be obtained with a prescription.

More about the procedure

The review of emergency contraceptives containing levonorgestrel and ulipristal acetate was initiated in January 2014 at the request of Sweden, under Article 31 of Directive 2001/83/EC.

The review was conducted by the Committee for Medicinal Products for Human Use (CHMP), the Committee responsible for questions concerning medicines for human use, which adopted the Agency's final opinion. The CHMP opinion was then forwarded to the European Commission, which issued a final legally binding decision on 30 September 2014.

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