Ethinylestradiol + levonorgestrel

NOT RECOMMENDED AS AN ESSENTIAL MEDICINE

ATC codes: G03AA07

Indication	Contact with health services for postcoital contraception ICD11 code: QA21.0
INN	Ethinylestradiol + levonorgestrel
Medicine type	Chemical agent
List type	Complementary
Formulations	**Oral > Solid:** 50 µg + 250 µg [4]
EML status history	First added in 1995 (TRS 867) Removed in 2003 (TRS 920)
Sex	Female
Age	Adolescents and adults
Therapeutic alternatives	Medicines within the same pharmacological class can be used
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Ethinylestradiol + levonorgestrel
DrugBank	Ethinylestradiol (Ethinyl Estradiol), Levonorgestrel

Summary of evidence and Expert Committee recommendations

The Committee considered a request submitted by the Department of Reproductive Health and Research, WHO, to delete the emergency contraceptive, ethinylestradiol + levonorgestrel (tablets, 50mcg + 250mcg (pack of four)) from the Model List. The Committee was informed that a levonorgestrel-only regimen is associated with significantly fewer side-effects (1,2) and, according to a large randomized double-blind multinational study organized by the Special Programme of Research, Development and Research Training in Human Reproduction, WHO, more effective as an emergency contraceptive than the combination regimen based on ethinylestradiol + levonorgestrel (four-pill pack) (3). Since the publication of the results of the WHO multinational trial in 1998, the levonorgestrel-only regimen has been registered in over 90 countries and some manufacturers have taken the combined emergency contraceptive pill (four-pill pack) off the market. The Committee was also informed about the results of a more recent randomized, double-blind trial which demonstrated that one dose of 1.5 mg levonorgestrel has the same efficacy, and without an increase in side-effects, as two 0.75 mg doses of levonorgestrel taken at an interval of 12 hours (4). In the light of this finding, one dose of 1.5mg levonorgestrel is now the recommended regimen for emergency contraception. At the present time, commercial packs contain two tablets of 0.75 mg levonorgestrel, but it is likely that single tablets of 1.5mg levonorgestrel will be available for this indication in the future. The Committee noted that the Model List currently contains two dosage forms for emergency contraception, namely: ethinylestradiol + levonorgestrel tablet, 50mcg + 250mcg (pack of four) and levonorgestrel tablet, 750mcg (pack of two). The Committee considered that the application for the deletion of the

former, that is the combination four-pill pack, is supported by a high level of clinical evidence of its inferiority relative to the levonorgestrel-only regimen, as summarized in the Cochrane Review (2). The Committee also acknowledged the better safety profile of the levonorgestrel-only regimen, confirmed statistically and clinically, and with fewer side effects. The relative risk of pregnancy (RR) for the levonorgestrel-only regimen compared with the four-pill combination was 0.80 with a 95% confidence interval (CI) of 0.74–0.86. Nausea (16.1% vs 46.5% and 23.1% vs 50.5%) and vomiting (2.7% vs 22.4% and 5.6% vs 18.8%) occurred less frequently with the levonorgestrel-only regimen ($P < 0.01$) (3). The Committee also considered the results of the recent WHO multicentre randomized trial of the two levonorgestrel-only based regimens (i.e. a single dose of 1.5mg as opposed to two doses of 0.75 mg taken 12 hours apart), involving 4071 women in 15 family planning clinics in 10 countries, which has demonstrated a high and equal efficacy of both regimens if taken within 5 days of unprotected coitus. The pregnancy rates were 1.5% (or 20 out of 1356) in women assigned single-dose levonorgestrel and 1.8% (or 24 out of 1356) in those prescribed the two-dose levonorgestrel regimen (no statistical difference, $p = 0.83$). The relative risk of pregnancy for single-dose levonorgestrel compared with two-dose levonorgestrel was 0.83 with 95% CI = 0.46–1.50 (4). The Committee concluded that there is good evidence in favour of the substitution of the two-dose regimen (0.75 mg 12 hours apart) with the single 1.5 mg dose of levonorgestrel; the use of a single dose simplifies the use of levonorgestrel for emergency contraception without an increase in side effects. On the basis of the evidence before it, the Committee recommended that a 1.5 mg tablet be added as a new dosage form of levonorgestrel and that ethinylestradiol + levonorgestrel (tablet, 50mcg + 250mcg, pack of four) be deleted from the Model List. 1. Ho PC, Kwan MSW. A prospective randomized comparison of levonorgestrel with the Yuzpe regimen in post-coital contraception. Human Reproduction, 1993, 8:389–392. 2. Cheng L et al. Interventions for emergency contraception [abstract]. In: The Cochrane Library [online database and CD-ROM], Issue 1. Oxford, Update Software, 2003:AB001324 (http://www.update-software.com/abstracts/ ab001324.htm). 3. Task Force on Post-ovulatory Methods of Fertility Regulation. Randomized controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. Lancet, 1998, 352:428–433. 4. von Hertzen H et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomized trial. Lancet, 2002, 360:1803–1810.

