

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 96N-0492]

Prescription Drug Products; Certain Combined Oral Contraceptives for Use as Postcoital Emergency Contraception

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that the Commissioner of Food and Drugs (the Commissioner) has concluded that certain combined oral contraceptives containing ethinyl estradiol and norgestrel or levonorgestrel are safe and effective for use as postcoital emergency contraception, and requests submission of new drug applications (NDA's) for this use. This notice is intended to encourage manufacturers to make this additional contraceptive option available.

ADDRESSES: Submit NDA's to the Food and Drug Administration, Center for Drug Evaluation and Research, Central Document Room, 12229 Wilkins Ave., Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Lisa D. Rarick, Center for Drug Evaluation and Research (HFD-580), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4260.

SUPPLEMENTARY INFORMATION:

I. Background

Combined oral contraceptives, which contain an estrogen and a progestin, were first approved in the United States in 1960 and in many other countries shortly thereafter. When taken daily for 3 weeks followed by a week without medication, these drugs provide effective contraception. They have become one of the most widely employed methods of pregnancy prevention, currently used by an estimated 11 million American women. In the period since the introduction of combined oral contraceptives, the amounts of estrogen and progestin have been reduced and explicit labeling guidance for safe use has been developed in response to extensive medical research. Consequently, combined oral contraceptives are now accepted as remarkably safe and effective when used as directed. There are more than 30 brands of FDA-approved oral contraceptives on the

American market that contain estrogens and progestins. These products contain estrogens and progestins in different amounts and have some differences in labeling, but all are considered to be safe and effective.

For several decades, estrogens and progestins have also been used, either separately or in combination, to prevent pregnancy in women who have unprotected intercourse as a result of rape, contraceptive failure, or lack of planning. Such drugs, when used for this purpose, are known as emergency contraceptive pills, or postcoital pills, or morning-after pills.

The best researched regimen for emergency contraceptive pills was first described in 1974 by Professor A. Albert Yuzpe of Canada (Ref. 18). The regimen consists of two tablets, each tablet containing 0.05 milligram (mg) of ethinyl estradiol and 0.50 mg of norgestrel, taken within 72 hours after unprotected intercourse; a second identical dose is to be taken 12 hours after the first dose. When used in this manner, the treatment is 75 percent effective in preventing pregnancy.

This regimen and the very similar regimens described below are widely used. The specific regimen described by Yuzpe is approved for use by the drug regulatory agencies of the United Kingdom, Germany, Sweden, Switzerland, and New Zealand. The approved products used in this regimen contain ethinyl estradiol and, as the progestin, either norgestrel or levonorgestrel.

The Yuzpe regimen and similar regimens have been used extensively in the United States in the last two decades, even though no products are approved and labeled for this use. The drugs are prescribed by hospital emergency rooms, reproductive health clinics, and university health centers. They are also prescribed, although less widely, by physicians in private practice. On February 14, 1996, the Reproductive Health Technologies Project established a hotline number (1-800-584-9911) to inform women about this contraceptive method and about providers in their local area.

Since the United Kingdom approved emergency contraceptive pills in 1984, more than 4 million prescriptions have been recorded. However, the actual use is much greater because providers have found it less expensive to provide tablets of identical drugs taken from products packaged as combined oral contraceptives. The use of combined oral contraceptives for emergency contraception in the United States can only be estimated because they are not approved for this indication, but the

results of a Kaiser Family Foundation survey reported at the June 28, 1996, meeting of FDA's Advisory Committee for Reproductive Health Drugs (the Advisory Committee) suggest that approximately 225,000 American women have used the method. A further indication of the extent of use is that over 25,000 calls were made to the hotline number (cited above) in the first 5 months of operation.

In November 1994, the Center for Reproductive Law & Policy filed a citizen petition asking FDA to require manufacturers of certain combined oral contraceptive products to amend their labeling and patient package inserts to include information regarding the use of these products for postcoital emergency contraception. Although FDA indicated that it had the authority to require that certain conditions of use be included in a product's labeling, it declined to exercise its discretion in this case to require the relabeling of these products for emergency contraception, and denied the petition. However, the agency decided to present the issue of the safety and effectiveness of combined oral contraceptives for postcoital emergency use to the Advisory Committee. The Advisory Committee met on June 28, 1996, to consider this issue and unanimously concluded that the four regimens below are safe and effective for postcoital emergency contraception. For the reasons described in section II. below, FDA agrees with this conclusion.

The four regimens for postcoital emergency contraception are as follows:

(1) For tablets that contain 0.05 mg of ethinyl estradiol and 0.50 mg of norgestrel, take 2 tablets within 72 hours after unprotected intercourse, then take 2 more tablets 12 hours after the first dose;

(2) For tablets that contain 0.03 mg of ethinyl estradiol and 0.30 mg of norgestrel, take 4 tablets within 72 hours after unprotected intercourse, then take 4 more tablets 12 hours after the first dose;

(3) For tablets that contain 0.03 mg of ethinyl estradiol and 0.15 mg of levonorgestrel, take 4 tablets within 72 hours after unprotected intercourse, then take 4 more tablets 12 hours after the first dose; and

(4) For tablets that contain 0.03 mg of ethinyl estradiol and 0.125 mg of levonorgestrel, take 4 tablets within 72 hours after unprotected intercourse, then take 4 more tablets 12 hours after the first dose.

The appendix to this notice provides information concerning the use of emergency contraceptive pills that might be useful to sponsors in drafting

physician and patient labeling for these products for this use.

II. Discussion

A. Safety

Experience with the approved products in Europe and New Zealand has demonstrated the regimens to be safe. At the Advisory Committee's June 28, 1996, meeting, Elizabeth Barden presented information from the British Medicines Control Agency that only six serious adverse reactions associated with these products for this use were reported to it from 1984 to 1996. Of these, only one occurred close enough to the time of administration to indicate that the reaction might be drug related.

Emergency contraceptive pills are not effective if the woman is pregnant; they act by delaying or inhibiting ovulation, and/or altering tubal transport of sperm and/or ova (thereby inhibiting fertilization), and/or altering the endometrium (thereby inhibiting implantation). Studies of combined oral contraceptives inadvertently taken early in pregnancy have not shown that the drugs have an adverse effect on the fetus, and warnings concerning such effects were removed from labeling several years ago. There is, therefore, no evidence that these drugs, taken in smaller total doses for a short period of time for emergency contraception, will have an adverse effect on an established pregnancy.

B. Effectiveness

There are numerous published articles that support the effectiveness of oral contraceptive pills for emergency use (Refs. 1, 3, 4, 7 through 14, 16 and 18 through 21). In 1996, Trussell, Ellertson, and Stewart reported a meta-analysis of 10 published articles on clinical trials of emergency contraceptive pills in which the number of pregnancies among women with regular menstrual cycles who used emergency contraception was compared to the expected number of pregnancies based on the cycle day of intercourse and published estimates of conception probabilities by cycle day (Ref. 9). Defining effectiveness as the percent reduction in the likelihood of pregnancy occurring, the authors found a range of effectiveness of 55.3 percent to 94.2 percent, with an average effectiveness of 74.0 percent. In other words, if 100 women have unprotected intercourse once during the second or third week of their menstrual cycle, about 8 will become pregnant, but if the same women use emergency contraception after intercourse, only 2 will become pregnant.

III. References

The following references have been placed on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Bagshaw, S. N., D. Edwards, and A. K. Tucker, "Ethinyl Oestradiol and D-Norgestrel Is an Effective Emergency Postcoital Contraceptive: A Report of Its Use in 1,200 Patients in a Family Planning Clinic," *Australian and New Zealand Journal of Obstetrics and Gynecology*, 28:137-140, 1988.
2. Delbanco, S., "1995 Kaiser Family Foundation Surveys on Emergency Contraceptive Pills: Knowledge and Attitudes among American Adults and Obstetrician/Gynecologists," Testimony before the FDA Reproductive Health Drugs Advisory Committee, June 28, 1996.
3. Fasoll, M., F. Parazzini, G. Cecchetti, and C. La Vecchia, "Post-coital Contraception: An Overview of Published Studies," *Contraception*, 39:459-468, 1989.
4. Glasier, A., "Postcoital Contraception," *Reproductive Medicine Review*, 2:75-84, 1993.
5. Glasier, A., et al., "Mifepristone (RU486) Compared with High-Dose Estrogen and Progestogen for Postcoital Emergency Contraception," *New England Journal of Medicine*, 327:1041-1044, 1992.
6. Haspels, A. A., and M. R. Van Santen, "New Aspects in Post-coital Contraception," in "Future Aspects in Contraception," edited by B. Runnebaum, T. Rabe, and L. Kiesel, MTP Press Limited, Boston, 1985.
7. Ho, P. C., and M. S. W. Kwan, "A Prospective Randomized Comparison of Levonorgestrel with the Yuzpe Regimen in Post-coital Contraception," *Human Reproduction*, 8:389-392, 1993.
8. Percival-Smith, R. K. L., and B. Abercrombie, "Postcoital Contraception with dl-Norgestrel/Ethinyl Estradiol Combination: Six Years Experience in a Student Medical Clinic," *Contraception*, 36:287-293, 1987.
9. Trussell, J., C. Ellertson, and F. Stewart, "The Effectiveness of the Yuzpe Regimen of Emergency Contraception," *Family Planning Perspectives*, 28:58-87, 1996.
10. Trussell, J., and F. Stewart, "The Effectiveness of Postcoital Hormonal Contraception," *Family Planning Perspectives*, 24:262-264, 1992.
11. Trussell, J., et al., "Emergency Contraceptive Pills: A Simple Proposal to Reduce Unintended Pregnancies," *Family Planning Perspectives*, 24:269-273, 1992.
12. Tully, B., "Postcoital Contraception—A Study," *British Journal of Family Planning*, 8:119-124, 1983.
13. Van Look, P. F. A., and H. von Hertzen, "Emergency Contraception," *British Medical Bulletin*, 49:158-170, 1993.
14. Van Santen, M. R., and A. Haspels, "Interception II: Postcoital Low-Dose Estrogens and Norgestrel Combination in 633 Women," *Contraception*, 31:275-293, 1985.
15. Webb, A., "Safety and Medical Contraindications," in "The Provision of

Emergency Hormonal Contraception," edited by D. Paintin, ch. 4, RCOG Press, London, 1995.

16. Webb, A., J. Russell, and M. Elstein, "Comparison of Yuzpe Regimen, Danazol, and Mifepristone (RU486) in Oral Postcoital Contraception," *British Medical Journal*, 305:927-931, 1992.

17. Webb, A., and D. Taberner, "Clotting Factors After Emergency Contraception," *Advances in Contraception*, 9:75-82, 1993.

18. Yuzpe, A. A., et al., "Post Coital Contraception—A Pilot Study," *Journal of Reproductive Medicine*, 13:53-58, 1974.

19. Yuzpe, A. A., R. Percival Smith, and A. Rademaker, "A Multicenter Clinical Investigation Employing Ethinyl Estradiol Combined With dl-Norgestrel as a Postcoital Contraceptive Agent," *Fertility and Sterility*, 37:508-513, 1982.

20. Yuzpe, A. A., and W. J. Lancee, "Ethinylestradiol and dl-Norgestrel as a Postcoital Contraceptive," *Fertility and Sterility*, 28:932-936, 1977.

21. Zuliani, G., U. F. Colombo, and R. Molla, "Hormonal Postcoital Contraception with an Ethinylestradiol-Norgestrel Combination and Two Danazol Regimens," *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 37:253-260, 1990.

IV. Conclusions

The Commissioner has concluded that combined oral contraceptives, taken initially within 72 hours of unprotected intercourse and providing a total of 0.10 or 0.12 mg of ethinyl estradiol and 0.50 or 0.60 mg of levonorgestrel in each of 2 doses separated by 12 hours, are safe and effective for use as postcoital emergency contraception. The Commissioner bases this conclusion on FDA's review of the published literature concerning this use (listed above), FDA's knowledge of the safety of combined oral contraceptives as currently labeled, and on the unanimous conclusion that these regimens are safe and effective made by the agency's Advisory Committee for Reproductive Health Drugs at its June 28, 1996, meeting. Because such combined oral contraceptives have not been labeled for this use or this dosage regimen, the Commissioner finds that these products are new drugs as defined in section 201(p)(1) and (p)(2) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)(1) and (p)(2)). Accordingly, approved NDA's are required as a condition of marketing.

FDA is prepared to accept NDA's for combined oral contraceptives appropriately labeled for use as postcoital emergency contraception under section 505(b)(2) of the act (21 U.S.C. 355(b)(2)) and part 314 (21 CFR part 314). Because of the publicly available safety and effectiveness data documenting the drugs' use, the safety and effectiveness requirements of § 314.50 may be met by citing the

published literature listed in the references in section III. of this document. The Commissioner advises that it is unnecessary to submit copies and reprints of the data cited in section III. of this document. Both the safety and effectiveness data upon which the Commissioner bases the above conclusions and the minutes of the Advisory Committee meeting are on file for public inspection in the Dockets Management Branch (address above). The Commissioner invites applicants to

submit any other pertinent studies and literature of which they are aware.

Dated: February 20, 1997.
David A. Kessler,
Commissioner of Food and Drugs.

Appendix

Use of Emergency Contraceptive Pills (ECP's)

ECP's consist of two doses of regular birth control pills containing estrogen and progestin. Taking ECP's provides a short, strong, burst of hormone exposure. Depending on where you are in your cycle

and when you had unprotected intercourse, using ECP's may prevent ovulation, disrupt fertilization, or inhibit implantation of a fertilized egg in the uterus.

How To Use ECP's

The oral contraceptive pills that can be used as ECP's are listed below. Take only one type of pill, not all of them. For example, if you use Ovral, you do not need Nordette. If you are getting your ECP's from a regular pack of birth control pills containing 28 pills (1 for every day), remember that the last 7 (green or pink) pills do not contain any hormones.

Brand Name	Pill Color	Number of pills to swallow within 72 hours after unprotected sex	Number of pills to swallow 12 hours later
Ovral	white	2	2
Lo/Ovral	white	4	4
Nordette	light orange	4	4
Levlen	light orange	4	4
Triphasil	yellow	4	4
Tri-Levlen	yellow	4	4

1. Swallow the first dose no later than 72 hours after having unprotected sex. Remember that the second dose must be taken 12 hours after the first dose. Taking the first dose at 3 p.m. would mean taking the second dose at 3 a.m. So take the first dose at a time that will make it convenient to take the second dose 12 hours later.

2. Swallow the second dose 12 hours after taking the first dose. Do not swallow any extra ECP's. More pills will probably not decrease the risk of pregnancy any further and will increase the risk of nausea.

Side Effects of ECP's

About half the women who take ECP's have temporary nausea. It is usually mild and should stop in a day or so. The risk of nausea may be reduced if you take a long-acting nonprescription anti-nausea medicine (such as meclizine) 30 minutes to 1 hour before taking each of the two doses of ECP's. About 20 percent of women who take ECP's vomit. If you vomit within an hour after taking either dose of ECP's, call your clinician to discuss whether to repeat that dose or to take anti-nausea medicine.

Before Taking ECP's

If you think you might have gotten pregnant last month, see your clinician before taking ECP's. Early pregnancy symptoms can include breast tenderness, nausea, or a previous period that was not quite normal.

If you have a serious medical problem, talk to your clinician before using ECP's.

After Taking ECP's

Your next menstrual period may start a few days earlier or later than usual. If your period does not start within 3 weeks, see your clinician for an exam and pregnancy test. If ECP's fail, or if you were already pregnant when you took ECP's, the fetus would be exposed to hormones. Studies of women who continued to take birth control pills after they unknowingly became pregnant do not show any evidence of harm to the fetus.

ECP's may not prevent an ectopic pregnancy (in the tubes or abdomen). Ectopic pregnancy is a medical emergency. In ectopic pregnancies, spotting and cramping pain usually begin shortly after the first missed

menstrual period. See your clinician immediately if you experience these symptoms.

After taking ECP's, get started as soon as you possibly can with a method of birth control you will be able to use every time you have sex. ECP's are meant for one-time, emergency protection. ECP's are not as effective as other forms of birth control. If you want to start or resume use of birth control pills after taking ECP's, consult your clinician. Protect yourself from Acquired Immune Deficiency Syndrome (AIDS) and other sexual infections as well as pregnancy. Use condoms every time you have sex if you think you may be at risk.

Source: Adapted (with permission) from Trussell, J., F. Stewart, F. Guest, and R. A. Hatcher, "Emergency Contraceptive Pills: A Simple Proposal To Reduce Unintended Pregnancies," *Family Planning Perspectives*, 24:269-273, 1992.

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