

Medical Officer Safety Review

I. Background:

Plan B was approved for use as an emergency contraceptive on July 28, 1999 and launched 8-23-99. The product contains only a progestin, levonorgestrel, in two single-dose tablets (each 0.75 mg). This differs from the first approved emergency contraception pills (ECPs) PrevenTM which contains four tablets, each with 0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol. The approved regimen for Plan B is two doses taken 12 hours apart. It should be started within 72 hours of unprotected intercourse.

The sponsor has submitted an application for the product to go OTC (over-the-counter). There are several questions that must be answered in order to determine whether a product is suitable for a prescription to OTC switch. These questions include, from a safety perspective:

1. Does the product have an acceptable margin of safety as based on prior prescription marketing experience?
2. Does the product have a low misuse and abuse potential?
3. Do the benefits from the OTC switch outweigh the risks?
4. Is the self-treatment product safe and effective during consumer use?

II. Safety Data:

A. Original NDA data:

The applicant in the original Plan B NDA presented clinical trial safety results from four general trial categories. These were:

1. Single Dose and Multiple Dose Clinical Pharmacology Studies
2. Two World Health Organization (WHO/HRP) sponsored comparative studies that were the main studies supporting efficacy and safety. The trials compared levonorgestrel (0.75 mg) to the Yuzpe regimen [levonorgestrel + ethinyl estradiol] for emergency contraception.
 - WHO/HRP 1998 – Study 92908: **the pivotal study for the NDA, N = 1,955**
 - Ho and Kwan 1993 – WHO/HRP Study 81107: **supportive study for the NDA, N = 834**
3. Three WHO/HRP-sponsored trials of routine postcoital contraception with the levonorgestrel 0.75 mg formulation manufactured by Gedeon Richter
 - WHO/HRP 1987 – Study 82906
 - WHO/HRP 1993 – Study 87908
 - He 1991 – WHO/HRP Study 84902
4. Fifteen small studies of oral levonorgestrel for routine or occasional postcoital contraceptive use, using a variety of regimens, doses, and formulations.*

*See Table 4 at the end of this review for a listing of several levonorgestrel studies for postcoital contraception.

Levonorgestrel, taken for postcoital contraception, is well tolerated and safe as shown by the extensive safety data from more than 15,000 women in the above studies using various doses of levonorgestrel for emergency contraception, occasional postcoital contraception, or routine postcoital contraception. The data in the NDA represented the bulk of both literature and unpublished study reports found as a result of an extensive literature search. The search did not uncover any serious adverse events, and the side effects reported were consistent across the studies. No serious adverse events were reported during the 1999 NDA review from three

ongoing studies of levonorgestrel or from introductory trials of Postinor-2 (levonorgestrel) in three countries. There were no thromboembolic events or ectopic pregnancies in these trials. One significant finding was that levonorgestrel was superior to the Yuzpe regimen [levonorgestrel + ethinyl estradiol] for the side effects of nausea and vomiting, and Plan B was thus labeled.

B. Postmarketing (PM) Safety Data and Levonorgestrel ECP Distribution:

1. Distribution/Use: Since the product launch in August 1999, the applicant estimates that 2.4 million women in the United States have used Plan B. From 7-28-02 to 7-27-03, 1,458,536 units of Plan B were sold; an estimated 80% were used by ~1.2 million women in the USA. Marketing began in Canada on 6-23-00; in the most recent reported year, the applicant estimates that 72,000 women used Plan B in Canada. In the UK, the applicant estimates that 2.1 million women have taken Levonelle (identical to Plan B) since February 2000. Patient exposure in France is estimated to be 1.8 million uses. Levonorgestrel for emergency contraception is available in 101 countries and is available without a prescription at the pharmacy in 33 of these 101 countries.

2. Applicant PM Data: The applicant compiled postmarketing data from a number of USA and global sources, including key European countries, Canada, and the WHO Drug Monitoring Program, to provide an assessment of the PM safety profile of levonorgestrel 0.75 mg tablets up to January 2003. There have been no reported deaths; most of the adverse events (AEs) attributed to the drug are mild and short-term. The most common AEs are nausea, abdominal pain, fatigue, headache, and changes in menstrual bleeding. In the 3-year period covered by the applicant's required Periodic Safety Updates¹ to the FDA and in their subsequent annual report, there have been 328 reported AEs. Pregnancy (123/328) and metrorrhagia (heavy bleeding; 64/328) are the two events most frequently reported. All of these events are consistent with the approved Plan B label and the proposed Plan B OTC labeling.

3. FDA PM Data: The Agency's Office of Drug Safety (ODS) was consulted and focused on the FDA Adverse Event Reporting System (AERS) and United Kingdom (UK) databases for adverse events reported up to 10-9-03.² There were no reports of death in women using postcoital levonorgestrel in either the AERS or the UK's database. The search identified 116 unduplicated cases; most of the reports involved non-serious expected (labeled) events. The most common non-serious events were: vaginal bleeding (26), unintended pregnancy (21), cramps/pain (11), and nausea/vomiting (11). There were 28 cases of unduplicated ectopic pregnancies (none occurred in the USA) which are discussed below. There were three unduplicated cases of convulsions, 10 cases of hypersensitivity, and 8 cases of possible pregnancy/fetal effects.

a. Ectopic Pregnancy Risk: With respect to pregnancy outcomes, the literature suggests an increased risk of ectopic pregnancy with progestin-only oral contraceptive pills that are taken on a regular daily basis. Based on the data from the sources discussed below there does not appear to be an increased risk of ectopic pregnancy with the use of levonorgestrel for emergency contraception or postcoital contraception.

i. FDA Office of Drug Safety reported postmarketing review: there were 28 unduplicated cases of ectopic pregnancy; none were from the USA; there were no deaths; 15 patients were hospitalized, and 10 had surgery. There were 12 cases from Gideon

¹ Current NDA submission, Volume 9, page 116.

² The ODS Postmarketing Safety Review dated October 31, 2003 is attached: see Subsection B

Richter (manufacturer of levonorgestrel) in Hungary without information on the country of origin, 10 from the UK, 3 from Israel, 1 from Sweden, China, and an unstated country.

Postmarketing data are hard to interpret because 1) the denominator (number of drug exposures or total number of pregnancies) is unknown, 2) the likelihood of reporting ectopic pregnancies (a serious adverse event) is greater than the likelihood of reporting pregnancies (since a pregnancy is a product failure and not actually an adverse event), and 3) there is considerable underreporting of AEs in general.

ii. Six large randomized clinical trials (RCTs) published in the medical literature: there are 7,893 evaluable subjects with 133 pregnancies and 2 ectopics, for an incidence of 1.5% ectopic pregnancies among total pregnancies. This is compelling data for the incidence of ectopic pregnancy associated with use of ECPs because RCTs are the "gold standard" with strict protocols and known numerators and denominators. The 1.5% incidence is consistent with the reported national rates of 12.4 and 19.7 per 1000 pregnancies [range 1.24 to 2.0%] in the UK and in the USA, respectively.^{3,4} These 6 clinical trials provide evidence that levonorgestrel-only ECPs do not increase the chance that a pregnancy will be ectopic. Moreover, because ECPs are at least 75% effective in preventing a pregnancy, ECPs also reduce a woman's absolute risk of an ectopic pregnancy. The data from the RCTs is summarized in Table 1 below:

Table 1.

Randomized Clinical Trial	Evaluable (n)	Pregnancies	Ectopic pregnancies (n)	Levonorgestrel dose (mg)
WHO 2002 ⁵	1356	24	1	0.75- 2 doses
	1356	20	0	1.5- single dose
Arowojolu et al. ⁶	545	7	0	0.75- 2 doses
	573	4	0	1.5- single dose
WHO 1998 ⁷	976	11	0	0.75- 2 doses
Wu et al. ⁸	643	20	0	0.75- 2 doses
Ho and Kwan ⁹ 1993	410	12	0	0.75- 2 doses
Ho et al. 2003 ¹⁰	2,030	35	1	0.75- 2 doses
TOTAL	7,889	133	2	

³ Rajkhowa M, et al. Trends in the incidence of ectopic pregnancy in England and Wales from 1966 to 1996. *Br J Obstet Gyn* 2000;107:369-74.

⁴ Ectopic pregnancies: USA data, 1990 to 1992. *Morb Mortal Wkly Report* 1995;44:46-48.

⁵ von Hertzen H, et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicenter randomized trial. *Lancet* 2002;360:1803-10.

⁶ Arowojolu AO, et al. Comparative evaluation of the effectiveness and safety of two regimens of levonorgestrel for emergency contraception in Nigerians. *Contraception* 2002;66:269-73.

⁷ Task Force on Post-ovulatory Methods of Fertility Regulation. Randomized controlled of levonorgestrel versus Yuzpe regimen of combined oral contraceptives for emergency contraception. *Lancet* 1998;352:428-433.

⁸ Wu S, et al. A randomized, double-blind, multicenter study on comparing levonorgestrel and mifepristone for emergency contraception [in Chinese]. *Zhonghua Fu Chan Ke Za Zhi* 1999;34:327-30. In *J of Fam Plan and Repro Health Care* 2003;29(4):249.

⁹ Ho PC, Kwan MSW. A prospective randomized comparison of levonorgestrel and the Yuzpe regimen in post-coital contraception. *Hum Reprod* 1993;8:389-92.

¹⁰ NDA submission, Volume 13/59, pages 047-048j. [13 pages]

- iii. Applicant reported postmarketing (UK Medicines Control Agency and French Health Authority) and US reports (summarized in Table 2 below): there were 340 pregnancies and 21 ectopic pregnancies (5.8%) reported to February 2003.¹¹

Table 2.

Country	Pregnancies (N)	Ectopics (N)	Ectopic % among total pregnancies
France (2-03)	29	8	21%
United Kingdom (1-03)	201	12	5.6%
United States (2-03)	110	1	0.9%
TOTAL	340	21	5.8%

The prescription label for Plan B has a subsection titled **Ectopic Pregnancy** in the WARNINGS Section. The following text is found in this section:

Ectopic pregnancies account for approximately 2% of reported pregnancies (19.7 per 1000 reported pregnancies). Up to 10% of pregnancies reported in clinical studies of routine use of progestin-only contraceptives are ectopic. A history of ectopic pregnancy need not be considered a contraindication to use of this emergency contraceptive method. Health providers, however, should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of lower abdominal pain after taking Plan B®.

The proposed OTC label for Plan B cautions women to be alert for symptoms that could be indicative of an ectopic pregnancy. There is no evidence that history of a previous ectopic pregnancy or tubal disease is a contraindication to use of Plan B or that the risk of an ectopic pregnancy is greater with the use of levonorgestrel emergency contraception.

- b. Fetal Risk:** In the original NDA, there were no reports of congenital abnormalities among women for whom the treatment failed or women mistakenly enrolled in studies who received the treatment after they were already pregnant. The FDA's ODS consultation found 3 cases of spontaneous abortion, 1 missed abortion, 1 inevitable abortion, and 3 reported European cases of congenital anomalies in pregnancies in women who had taken levonorgestrel ECPs. Given that spontaneous abortions have been reported to occur in 10-15% of clinically recognized pregnancies¹², these reported events appear to be below the expected rate in the general population. In one congenital anomaly case, the woman also received abdominal X-rays at gestational week 12/40. With the applicant's estimated patient use of Plan B in 2.4 million USA and 2.1 million UK women and the reduced risk of pregnancy of 1.1% in these women, one would expect ~49,500 unplanned pregnancies. These three reported cases are well below the expected 0.85% incidence of these congenital anomalies.¹³ It is unlikely that the Plan B exposure was a causative agent of the anomalies. The FDA did a review¹⁴

¹¹ Current NDA submission, Volume 9, page 119.

¹² ACOG Practice Bulletin, Clinical Management Guidelines for Obstetrician-Gynecologists; February 2001, No. 24: 1.

¹³ ACOG Practice Bulletin. Prenatal Diagnosis of Fetal Chromosomal Abnormalities. May 2001; No. 27:1-11.

¹⁴ See appended report dated June 26, 2002: Subsection C.

of the teratogenic risk of accidental use of contraceptive hormones early in pregnancy and concluded that there is not an association with adverse fetal or pregnancy outcomes. No studies have been large enough to quantify the teratogenic risk among the small number of pregnancies that follow the use of ECPs. However, observations that there is no increase in birth defects among pregnancies exposed to daily use of combined oral contraceptives are reassuring.¹⁵

- c. **Allergic Reactions:** The ODS consultation for levonorgestrel emergency contraception identified ten unduplicated cases of hypersensitivity reactions, three of which occurred in the United States. Events ranged from minor localized rashes to urticaria, from localized edema to systemic edema, and included two cases of difficulty breathing [one of those cases occurred in a woman who clearly had a history of an underlying pulmonary disorder given her list of concomitant medications (Buspar, Flovent, Singulaire, Seravent); so it is unclear whether the condition was levonorgestrel related]. The time of onset was stated in 8 reports and ranged from 4 hours to 2 days after taking the drug. Although 7 cases were marked "life-threatening," none of the women stayed overnight in the hospital and the narratives provided in the reports did not clearly reflect a life-threatening event. Four of the women had taken concomitant medications, including 2 women on antibiotics, that could have caused the reported reactions.

III. Misuse and Abuse:

A. Overdose:

Overdosing is unlikely, since Plan B is packaged as a single course of treatment and is relatively expensive. In clinical trials in Eastern Europe between 1976-87 of women using up to 8 levonorgestrel 0.75 mg tablets in a single menstrual cycle and up to four 0.75 mg tablets in a single day, one SAE (an ectopic pregnancy) was reported. The applicant's review of the Toxic Exposure Surveillance System (TESS) found few reports on Plan B and none that resulted in death or serious illness. In reviewing the medical literature on advance provision, there were no cases of overdose or excessive use. There are no reports of any person overdosing on this product in the Agency's AERS database.

B. Repeat Use:

Studies investigating how often women use ECPs have found that using it more than four times in one year is uncommon. A study of general practice patients in the UK found that less than one percent of ECPs users requested ECPs more than three times a year.¹⁶ International studies indicate that advance provision of ECPs does not lead women to replace their regular method of contraception with ECPs.¹⁷⁻¹⁸ Studies show that women with easier access to ECPs are more likely to use it when needed, potentially reducing unintended pregnancies and the number of induced abortions.¹⁹

¹⁵ Bracken MB. Oral contraception and congenital malformations in offspring: a review and meta-analysis of the prospective studies. *Obstetrics Gynecology* 1990;76:552-57.

¹⁶ Rowlands S, Lawrenson R. Repeated use of hormonal emergency contraception by younger women in the UK. *Br J Fam Plan* 2000;26:138-43.

¹⁷ Glasier A, Baird D. The effects of self-administering emergency contraception. *NEJM* 1998;339(1):1-4.

¹⁸ Turner AN, Ellertson C. How safe is emergency contraception? *Drug Safety* 2002;25(10):695-706.

¹⁹ Grimes DA. Correspondence: replies. *NEJM* 2003;348(1):83.

Guidelines from the World Health Organization, American College of Obstetricians and Gynecologists, and the American Society for Emergency Contraception clearly state that although frequent use of ECPs is not recommended, repeat use may be offered. There are no medical contraindications (except allergy to levonorgestrel) to Plan B.

C. Use During Pregnancy:

There is no evidence that a woman's use of Plan B while she is pregnant will result in abortion. Risk to the fetus if exposed to Plan B during pregnancy was addressed in the Fetal Risk subsection of the Post Marketing Safety section above, and in the appended review of teratogenic risk. The approved ECPs have been shown to inhibit ovulation depending on when in the menstrual cycle they are taken. It is believed that they may also interfere with the actual process of fertilization by interfering with transport of the egg or sperm or with the necessary changes that the sperm must undergo to be able to fertilize an egg. Levonorgestrel, depending on dose and the time it is administered in the menstrual cycle, does alter the endometrium, but there is little direct evidence that interference with implantation is the principal mechanism of action.^{20,21} Since most of the risk of pregnancy is concentrated in the days leading up to and including the day of ovulation, and since a direct effect on the process of ovulation has been clearly demonstrated, it is likely that the method works primarily prior to fertilization. The fact that the method is more effective the sooner it is used also argues against post-fertilization modes of action. There is no clear evidence that ECPs will prevent pregnancy after implantation and will interrupt an already-established pregnancy.²² The inclusion of pregnancy as a contraindication in the Plan B label is related not to safety, but to inform the consumer that the product will not interrupt an established pregnancy.

IV. Contraindications:

There are no absolute contraindications to the use of hormonal emergency contraception.²³ The labeled contraindications for prescription Plan B include 1) known or suspected pregnancy [not a safety issue; listed because the product will not interrupt a pregnancy], 2) hypersensitivity to any component of the product, and 3) undiagnosed abnormal genital bleeding. These three conditions are listed in the class label for progestin-only contraceptive pills that are taken daily without interruption for routine contraception. The Plan B prescription label states "It is not known whether these same conditions apply to the Plan B regimen consisting of the emergency use of two progestin pills." The terms 'undiagnosed abnormal genital bleeding' or 'unexplained vaginal bleeding' are not, in fact, a medically founded contraindication for using Plan B; the applicant has proposed that this condition be removed from the OTC label. The Reproductive Division agrees with the applicant's request.

V. Safety of Advanced Provision and Pharmacy Provision

Currently in the United States, Plan B is available by prescription from a health care provider in all states, and directly from qualified pharmacists ("behind the counter") in 5 states. Direct access

²⁰ Marions L, et al. Emergency contraception with mifepristone and Levonorgestrel: Mechanism of Action. *Obstetrics and Gynecology* July 2002;100(1):65-71.

²¹ Durand, M, et al. On the mechanisms of action of short-term levonorgestrel administration in emergency contraception. *Contraception* 2001;64:227-34.

²² Rivera R, et al. The mechanism of action of hormonal contraceptives and IUDs. *AJOG Reviews. Am J Obstetrics Gynecology* 1999;181(5):1263-69.

²³ Westoff C. Emergency Contraception: clinical practice. *NEJM* November 6, 2003;349:1830-35.

from a pharmacist was started as a pilot program in Washington in 1997. Washington now has ~300 pharmacies with ~1,700 trained pharmacists in the statewide program. Washington is the only state with government reimbursement of a pharmacist for counseling associated with purchasing ECPs. Other states with pharmacy provision of ECPs are California (1-02), Alaska (3-02), New Mexico (12-02), and Hawaii (6-03).

Worldwide, levonorgestrel 0.75 mg tablets are now available in 101 countries²⁴ and on a nonprescription basis from pharmacies in 33 of these countries. ECPs are available over-the-counter (OTC) in Norway, Sweden and in at least three provinces²⁵ in Canada.

The other method of easier access to ECPs is advanced prescription or provision of the product. As access to ECPs becomes easier through advance provision or pharmacy availability or possible OTC status, several studies have concluded that greater availability does not result in misuse or raise safety concerns in terms of serious adverse events, hospitalization, or prolonged or severe labeled adverse events.²⁶ To date, there is no comprehensive study that has evaluated the USA pharmacy experiences or has documented any safety concerns in that setting.

VII. Overall Safety Conclusions for Levonorgestrel ECPs:

From an extensive review of published studies of RCTs, postmarketing data, the medical literature, and large safety databases, it appears that levonorgestrel emergency contraception pills, Plan B and the identical products worldwide, have an acceptable margin of safety with a low misuse and abuse potential. The individual can easily determine their need for emergency contraception and the treatment is easy to use (two tablets 12 hours apart for all women). There is no definite contraindication to Plan B except an established allergy to levonorgestrel, which has been rarely reported over the 25 years that levonorgestrel has been taken by millions of women using a combination hormonal oral contraceptive or ECPs containing levonorgestrel. There are no clear dangers to a fetus or a pregnancy should the drug be taken when a woman is already pregnant. This safety profile must be weighed against the benefit that emergency contraception affords women a second chance to avoid unwanted or unplanned pregnancies. Because emergency contraception is more effective in preventing pregnancy the earlier it is taken after unprotected sexual intercourse, over the counter status should enhance benefit by providing more timely access to the product than through prescription.²⁷

VIII. Labeling Recommendations

The applicant, in response to their Label Comprehension Study, made labeling changes before the Actual Use Study was started. From a safety perspective the following labeling messages are recommended:

- Do not take Plan B if you are allergic to levonorgestrel or any ingredient in Plan B
- Contact your health care provider if you experience the following:
 - Severe stomach or pelvic pain, since this can be a warning sign of a tubal (ectopic) pregnancy

²⁴ Applicant Advisory Committee Briefing Document.

²⁵ Email sent to Vyta Senikas, Exec. VP, The Society of Ob/Gyn of Canada, on 10-24-03 for further details.

²⁶ See FDA Review of Behavior Study Literature and applicant's Integrated Summary of Safety (Volume 9 of 59 volume NDA submission).

²⁷ This conclusion was clearly demonstrated in the FDA review of the original efficacy data from the comparative WHO multicenter Study 92808 submitted in the Plan B application in 1999, and has been substantiated by several articles in the peer-reviewed medical literature.

- No menstrual period in two weeks
- Any severe symptoms or symptoms that last more than 48 hours
- ECPs do not protect against sexually transmitted infections (STIs); condoms should be used if you are at risk for STIs

The Division of Reproductive and Urologic Drug Products agrees with the applicant that these are critical messages for inclusion in the OTC label, and also agrees that "unusual or abnormal vaginal bleeding" is not a contraindication and should be removed from the label.

From an efficacy perspective it is important for the label to carry messages regarding appropriate timing of administration:

- **ECPs should be taken as soon as possible after unprotected sex**, since ECPs are more effective the earlier they are initiated^{28,27}
- The second dose should be taken 12 hours after the first dose

Timing of the second dose was one issue raised during the review of the Actual Use Study. In the original NDA review, there were 37 pregnancies (10 with levonorgestrel; 27 with Yuzpe); all of these subjects took their second dose within 11-12 hours of the first dose. In contrast there were 86 of 1955 evaluable subjects who took their second dose late (by at least 6 hours) and none of these women became pregnant. Only 7 of 1955 women did not take the second dose within 24 hours and none of these women became pregnant. There have been two large, double-blind, randomized studies with 2712²⁹ and 1118³⁰ evaluable women that compared administering levonorgestrel as a single dose of 1.5 mg to the two dose 12-hour regimen of 0.75 mg levonorgestrel. In both studies, the contraceptive effectiveness was better in the single dose regimen (20/1356 and 4/573 pregnancies) than in the two-dose regimen (24/1356 and 7/545 pregnancies). (See Table 3 below.) The single dose regimen was also shown to be safe, and the side effects did not differ greatly between groups.

Table 3

Trial	Single 1.5mg dose Pregnancies/ evaluable N	Two 0.75mg doses (12 hr) Pregnancies/ evaluable N
Von Hertzen et al. (WHO 2002)	20/1356	24/1356
Arowojolu et al.	4/573	7/545

Timing of the first dose has also been examined. There have been two studies that have limited data on taking the first dose at a later time (72 to 120 hours).^{31,32} Both studies showed that ECPs have a favorable success rate after 72 hours, with a pregnancy rate that is lower than would be expected if no contraception were administered.

These data support the conclusion that, although the recommended time for the second dose is 12 hours, it can be taken sooner than 12 hours or later (by at least 6 hours). There are also data in the

²⁸ Task Force on Post-Ovulatory Methods of Fertility Regulation. Randomized controlled trial of levonorgestrel versus the Yuzpe regimen of combination oral contraceptives for emergency contraception. *Lancet*. 1998; 352:428-33.

²⁹ Von Hertzen H, et al. *Op. cit. Lancet* 2002(Dec).

³⁰ Arowojolu AO, et al. *Op. cit. Contraception* 2002

³¹ Von Hertzen H, et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicenter randomized trial. *Lancet* 2002(Dec.);360:1803-10.

³² Rodrigues J, et al. Effectiveness of ECPs between 72 and 120 hours after unprotected sexual intercourse. *Am J Obstetrics Gynecology* 2001;184:531-37.

literature that suggest Plan B may be taken up to 5 days (120 hours) after unprotected sexual intercourse.

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11-15-03

Table 4 Studies of Levonorgestrel Taken After Intercourse for Postcoital Contraception: Regimens Used

STUDY	REGIMEN
WHO/HRP-sponsored multicenter studies: single 0.75 mg dose of levonorgestrel	
WHO/HRP 1987 – Study 82906 International	One 0.75 mg tablet within 8 hours after the first coital act in the periovulatory period, then one tablet 24 hours later, then one tablet after each coital act, but no more than one tablet per 24 hours.
He, China 1991	One 0.75 mg tablet within 8 hours after the first coital act in the periovulatory period, then one tablet 24 hours later, then one tablet after each coital act, but no more than one tablet per 24 hours.
WHO/HRP 1993 – Study 87908 International	One 0.75 mg tablet within one hour after each coital act, but no more than one tablet within a 3-hour period.
Other studies of levonorgestrel, 0.75 mg	
Seregely, Hungary (multicenter 16 small studies)	One 0.75 mg tablet within one hour after each coitus, but no more than one tablet per 3-hour period. In cases of “clustered coitions”, 1 tablet after the first act, another three hours later, and a third the following day.
Chernev Bulgaria	One 0.75 mg tablet within one hour after each coital act; no more than four tablets per month.
Szczurowicz, Poland	0.75 mg tablets; up to 4 per cycle
Nirapathpongporn Thailand	One 0.75 mg tablet within one hour after each coital act, but no more than one tablet within any three hour period. In cases of multiple acts, one tablet within one hour after the first act, a second tablet 3 hours later, and a third tablet the next morning.
Czekanowski Poland	One 0.75 mg tablet within one hour after each coital act, but no more than one tablet within any 3-hour period. In cases of multiple acts, one tablet within one hour after the first act, a second tablet 3 hours later, and a third tablet the next morning.
Klawe Hungary	0.75 mg tablets; regimen not stated.
Orley Hungary	One 0.75 mg tablet within one hour after intercourse. In case of repeated intercourse, one more tablet three hours later.
Sas, Hungary	One 0.75 mg tablet within one hour after each coital act
Other studies: using various dose levels of levonorgestrel	
Kesserü Peru	One tablet (0.15, 0.25, 0.30, 0.35, 0.40 mg) within one hour after each coital act.
Moggia Argentina	One 0.35 mg tablet within one hour after each coital act.
Echeverry Columbia	1.0 mg within 8 hours after intercourse, but no more than one tablet in an 8 hour period
Hurtado Peru	Various doses; regimens not stated. (Original efficacy data from files of Schering A.G.)
Larrañaga, Peru	One 1.0 mg tablet immediately after intercourse
Canzler East Germany	Group A: One 0.4 mg tablet within 12 hours after each coital act. Group B: Two 0.25 mg tablets immediately before and one 0.25 mg tablet 8 hours after each coital act