CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 21045

MEDICAL REVIEW(S)

JUN 23 1999

Medical Officer Review of NDA 21,045: Levonorgestrel 0.75 mg tablets (2) for Emergency Contraception

Investigational product: Levonorgestrel

Indication: Emergency contraception

Design: Multicenter, double blind, randomized, active-controlled comparison of two doses of levonorgestrel 0.75 mg with the Yuzpe regimen (two doses of ethinyl estradiol 0.1 mg + levonorgestrel 0.5 mg) within 72 hours after a single act of unprotected coitus in ~2000 women.

Sponsor: Women's Capital Corporation, Kirkland, WA and Washington, DC

Protocol Identification: WHO/HRP 1998 – Study 92908. A prospective, randomized, multicenter study to compare the Yuzpe regimen with levonorgestrel in emergency postcoital contraception.

Study initiation date: 14 July 1995

Study completion date: 31 July 1997

Name of sponsor signatory: Sharon Camp, Ph.D.

The study was performed in compliance with ethical guidelines that have their origin within the Declaration of Helsinki. Essential documents have been archived at World Health Organization, Geneva and tabulations have been archived at Family Health International, Research Triangle Park, NC, and at Women's Capital Corporation, Kirkland, WA.

CDER stamp date: January 29, 1999

CDER due date: July 29, 1999

MO Review completed: June 22, 1999

Related INDs and NDAs: IND and NDA 20,946

Additional reports: UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, Geneva, Switzerland: Research Group on Postovulatory Methods for Fertility Regulation: Study 92908, September 1997.

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LIST OF ABBREVIATIONS

AC	Advisory Committee
BMI	body mass index
CI	confidence interval
COC	combined oral contraceptive
CRF	case report form
DRUDP	Division of Reproductive/Urology Drug Products
EC	emergency contraception
ECP	emergency contraception pill
EE	ethinyl estradiol
FDA	Food and Drug Administration
FHI	Family Health International
HCG	human chorionic gonadotropin
ICC	International Computer Center
IRB	institutional review board
IUD	intrauterine device
LNG	Levonorgestrel
mcg	micrograms
mg	milligrams
MO	medical officer
MOR	medical officer review
POP	Progestin-only pill
RR	relative risk
WCC	Women's Capital Corporation
WHO	World Health Organization
WHO/HRP	United Nations/World Health Organization/World Bank Special Programme of Research, Development and Research Training in Human Reproduction
YZ	Yuzpe regimen (for emergency contraception)

1.0 Introduction

Emergency contraception (EC) is the use of a drug or device to prevent pregnancy within a few hours to a few days after unprotected sexual intercourse. Over the last two decades, a variety of approaches have been evaluated, including high-doses of estrogen, estrogen combined with progestin, progestin alone, antiprogestational agents such as mifepristone (RU 486) and intrauterine devices (IUDs) (Glasier: *NEJM* 1997). One of the most popular and effective choices for EC has been the Yuzpe regimen consisting of 4 tablets, each containing 0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol. Two tablets are taken within 72 hours of unprotected intercourse, and two more are taken 12 hours later.

Throughout this medical officer review (MOR), the terms "emergency contraception" and "emergency postcoital contraception" refer to the one-time use of a contraceptive drug or device to prevent pregnancy within 72 hours of unprotected sex or a contraceptive accident. "Postcoital contraception" as used in this review and the sponsor's integrated summaries, and as generally used in the literature, is a broader term covering various patterns of postcoital use of a drug to prevent pregnancy, including experimental drugs which might disrupt implantation or the progression of an early pregnancy. "Occasional postcoital contraception" refers to the use of a contraceptive drug immediately after each coitus by women with low coital frequency. Postinor (levonorgestrel 0.75 mg, manufactured by Chemical Works Gedeon Richter, Budapest, Hungary) is marketed for this indication in 34 countries in packages of four or ten tablets. "Routine postcoital contraception" refers to the immediate postcoital use of a contraceptive drug by sexually active women as their only method of contraception, an experimental contraceptive method no longer under investigation. Since the pivotal trials for this NDA refer to "emergency contraception," this will be the focus of the MOR.

Norgestrel and levonorgestrel are the only progestins that have been evaluated for emergency contraceptive use. Levonorgestrel is referred to as D-norgestrel in a number of published papers. It is also referred to as *d*-norgestrel (where the *d* is italicized). Levonorgestrel is the biologically active enantiomer of the racemic mixture, norgestrel. Half of a given dose of norgestrel, by weight, is considered the equivalent dose of levonorgestrel. The active enantiomer, levonorgestrel, has strong progestational and no estrogenic activity.

Levonorgestrel (or norgestrel) is the active progestin ingredient in 10 combined oral contraceptives (COC), approved for sale in the United States. Such COC products, containing a combination of the estrogen ethinyl estradiol and either norgestrel or levonorgestrel, were declared by the FDA Advisory Committee (AC) in 1997 to be safe and effective for emergency contraception. Norgestrel (0.075 mg) is the active ingredient in a progestin-only oral contraceptive, Ovrette™, marketed in the United States by Wyeth-Ayerst. Levonorgestrel is also used in the contraceptive subdermal implant Norplant™, which releases approximately 30 micrograms daily over a five-year period.

Since the early 1970s, investigators have studied the use of levonorgestrel for postcoital contraception. Levonorgestrel 0.75 mg tablets are currently marketed as Postinor in 34 countries for routine postcoital contraception by women with low coital frequency (less than four coital acts a month). The manufacturer's prescribing information for Postinor for routine postcoital contraception instructs users to take one tablet immediately after unprotected intercourse, followed by one tablet eight hours later in the case of repeated intercourse. The sponsor, Women's Capital Corporation (WCC), estimates that Postinor tablets have been sold since the drug product was first approved in 1980. Postinor-2 (identical to Plan B) is approved in three of these 34 countries for emergency contraception. The Postinor-2 regimen consists of two tablets of levonorgestrel 0.75 mg, one taken within 72 hours of unprotected intercourse, and the second taken 12 hours later.

Beginning in the early 1990s, investigators recognized the potential of levonorgestrel as an emergency contraceptive in place of the standard Yuzpe regimen of combined higher-dose oral contraceptive pills. For this narrower indication of EC, the product would be utilized principally as a back-up method for women relying on barrier contraceptives, such as condoms or diaphragms, or as a bridge to a more effective method of long-term contraception for women initiating sexual activity without adequate preparation. In recent

years, the United Nations/World Health Organization/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (WHO/HRP) has sponsored two controlled double-blind studies of levonorgestrel 0.75 mg tablets for emergency contraception. Both studies have been published (WHO/HRP Study 92908 in *Lancet*, 1998; Ho and Kwan in *Human Reproduction*, 1993). The first of these studies, conducted by Ho and Kwan, was a single center, randomized trial of levonorgestrel compared with the Yuzpe regimen, in women requesting emergency contraception within 48 hours of unprotected intercourse. Levonorgestrel was as effective as the Yuzpe regimen, and was associated with less nausea and vomiting.

Based on the findings of Ho and Kwan, WHO/HRP conducted a multicenter, randomized, double-blind study to assess the efficacy of levonorgestrel 0.75 mg tablets taken 12 hours apart for emergency contraception in women presenting within 72 hours after a single act of unprotected sex. This second large study, carried out world-wide between July 1995 and July 1997, is the primary pivotal study for this NDA since the study data is available for interpretation and audit. The Ho and Kwan study is considered supportive as its case review forms (CRFs) are not available.

2.0 Background

2.1 Regulatory History

In 1996, at an Advisory Committee (AC) focusing on the issue of emergency contraception, the FDA concluded that the "Yuzpe regimen" of certain combined oral contraceptive formulations containing ethinyl estradiol and levonorgestrel (or norgestrel) was safe and effective for use as emergency contraceptives (*Federal Register* 62:8610-12, 2/25/97). In the concluding statements of this document it was stated 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 emergency contraception."

A wide number of currently available combined oral contraceptive formulations are, according to the FDA decision, acceptable for off-label emergency contraceptive use. At the time of the AC in 1996, however, there were no approved products in the USA for emergency contraception.

In 1997, while oral contraceptive pills containing ethinyl estradiol and levonorgestrel (or norgestrel) were available in virtually every country for COC indications, the Yuzpe regimen packaged specifically for emergency contraceptive use was available only in the United Kingdom, Germany, Sweden, Switzerland, South Africa, Finland, Norway, and Denmark. On September 2, 1998, the FDA approved NDA 20,946 (the first EC regimen approved in the United States), for the Preven™ Emergency Contraceptive Kit. The product contains four emergency contraception pills, a urine pregnancy test, and a patient information book. Each pill consists of 0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol. Two tablets are taken within 72 hours of unprotected intercourse, and two more are taken 12 hours later. This is identical to the Yuzpe regimen. No clinical trial data were required because of the 1996 AC decision. A product label was created which described the safe and effective use of the Preven™ product for the indication of emergency contraception.

Beginning in the early 1990s, WHO/HRP fielded two well-controlled studies of levonorgestrel 0.75 mg specifically for emergency contraception. The single center study by Ho and Kwan in Hong Kong showed that levonorgestrel was better tolerated than the Yuzpe regimen, and was as effective (Ho and Kwan 1993). The results prompted WHO/HRP to launch a larger multicenter study (Study 92908) in order to confirm the findings of Ho and Kwan. This multicenter 14-country study serves as the pivotal study for this NDA, as agreed to at meetings in March 1997 and April 1998 between WCC and the Division of Reproductive and Urologic Drug Products (DRUDP). Throughout this MOR the "WHO/HRP 1998 – Study 92908" is referred to as the "Pivotal Study" or "Study 92908". The earlier Ho and Kwan study is provided as supporting evidence. Earlier studies of levonorgestrel for routine and occasional postcoital contraception

are submitted to provide a broader view of the drug's use in postcoital contraception over nearly three decades.

Reflecting agreements reached with the FDA in March of 1997, the primary safety analysis for the pivotal study would be a test of superiority of levonorgestrel *versus* Yuzpe relative to the risk of participants experiencing 1) vomiting and/or 2) nausea (within seven days of treatment). These tests would be performed using two-sided hypothesis tests at the 0.05 significance level on an intent-to-treat basis, using a Bonferroni correction to adjust for multiple testing.

In a pre-NDA meeting with the FDA on 13 April 1998, FHI proposed a revised analysis of the primary endpoints for efficacy and safety. FHI prepared the revised plan in February 1998, before unblinding the data. WCC submitted NDA 21,045 on January 29, 1999, and it has been granted a 6-month priority review.

2.2 Clinical Background for Emergency Contraception

Use of emergency contraception was first reported in the mid-1960s by a Dutch physician, initiating what became the first standard regimen for emergency use of hormones to prevent unwanted pregnancy following unprotected sex. The regimen consisted of five consecutive daily doses of 5.0 mg ethinyl estradiol. Through the decade of the 1960s, other high-dose estrogens (conjugated estrogens or the non-steroidal estrogen diethylstilbestrol) were also used for emergency contraception. While high-dose estrogens are effective, their use is associated with a high incidence of side effects, notably nausea and vomiting.

In 1972, Dr. Albert Yuzpe and colleagues evaluated a combination of ethinyl estradiol and norgestrel as a potential emergency contraception regimen. The highest success rates were achieved in trials using two doses of 0.1 mg ethinyl estradiol and 1 mg norgestrel administered 12 hours apart, and limited to women reporting coitus within the previous 72 hours (Yuzpe 1977 and 1982). Since the 70's, numerous other studies have been published which support the efficacy of combined therapy of a total dose of 0.2 mg ethinyl estradiol in combination with either 2.0 mg norgestrel or 1.0 mg levonorgestrel (Glasier 1997). Although the Yuzpe regimen causes fewer side effects than the earlier high-dose estrogen treatment, the incidence of nausea (about 50%), and that of vomiting (about 20%) remain substantial. Some clinicians prescribe concomitant anti-emetics, but there are no data to support this practice and there are no pharmacokinetic studies of drug interactions between the Yuzpe regimen and anti-emetics.

During the 1970's, a number of studies were undertaken in South America, with partial support from the German pharmaceutical company Schering AG, to test the efficacy of various progestins, including levonorgestrel, given alone for routine postcoital contraception by sexually active married women. Doses ranging from 0.15 mg to 1.0 mg were tested on over 7,000 women (Moggia 1974, Echeverry 1974, Kesserü 1973, Hurtado 1975). Schering eventually concluded that the contraceptive method was unsuitable because of the high incidence of menstrual cycle disturbances. Between 1975 and 1984, a series of clinical studies in Eastern Europe with levonorgestrel manufactured by showed that occasional postcoital use could be successful in women with infrequent intercourse (Seregély 1982).

Beginning in the early 1990s, WHO/HRP fielded two well-controlled studies of levonorgestrel 0.75 mg for emergency contraception using the product manufactured in Hungary. The single center study by Ho and Kwan in Hong Kong showed that levonorgestrel appeared to be better tolerated than the Yuzpe regimen, and was as effective (Ho and Kwan 1993). The results prompted WHO/HRP to launch the larger multicenter study (Study 92908) enrolling almost 2000 women in 14 countries in order to confirm the findings of Ho and Kwan.

2.3 Related INDs and NDAs

IND and NDA 20,946 are directly related to emergency contraception. IND dates back to stamp date 7/20/94 and contains the original WCC application for the current NDA. The IND consists primarily of general correspondence, chemistry information, and requests for information; it does not

contain a protocol review of the WHO Pivotal Study 92908. NDA 20,946 is the above mentioned application for the Preven™ product approved in September 1998 for emergency contraception.

2.4 International and Marketing Experience

Postinor-2 is the same product as Plan B (2 tablets, levonorgestrel 0.75 mg) and is marketed in Europe for emergency contraception. In 1997, WCC wrote to the Director of Medical Affairs at manufacturer of the drug to be marketed, to ask about any reported adverse events and other safety information related to Postinor. WCC was informed that no adverse event reports were on file in the Medical Department, which retains records only for the prior five years. In May 1997, WCC also wrote to the WHO/HRP Collaborating Centre for International Drug Monitoring. The WHO/HRP database for adverse reaction reports about Postinor produced only one report. (See Section 8.3. "Other Potentially Serious Adverse Events.")

In May 1998, WCC wrote to national drug monitoring agencies in Cuba, Czech Republic, Hungary, Bulgaria, Malaysia, Romania, and Thailand asking for complete information on all adverse reactions to Postinor which may have been reported to the pharmacovigilance systems existing in these countries. The letter included the FDA definition of "adverse drug experience." As of June 1998, WCC had received no reports of adverse events as a result of these inquires.

Reviewer's comment: It is actually concerning and unusual for any drug product that despite five years of marketing information, there was not a single adverse event reported to and only one to the WHO/HRP database. It is possible that the postmarketing data collection systems in place in the seven listed foreign countries may not provide very reliable post-marketing safety information.

3.0 Description of Clinical Data Sources for Efficacy and Safety

3.1 General Data Sources

Efficacy results were presented by the sponsor separately in three general categories. These were: 1) three clinical studies for emergency contraception, 2) three multicenter clinical studies of routine postcoital contraception using levonorgestrel 0.75 mg manufactured by and 3) 16 small studies of oral levonorgestrel for routine or occasional contraceptive use, with a variety of regimens, doses, and formulations.

The three clinical studies for emergency contraception are listed below:

- Two WHO/HRP-sponsored-studies of levonorgestrel for emergency contraception, using Postinor (levonorgestrel 0.75 mg), manufactured by
  - WHO/HRP 1998 – Study 92908
  - Ho and Kwan 1993 – WHO/HRP Study 81107
- One retrospective uncontrolled German study, at a lower dose

Safety results were presented by the sponsor in five general categories. These are:

1) Single Dose and Multiple Dose Clinical Pharmacology Studies

- WCC-PK001
- Three published foreign studies using levonorgestrel tablets 0.75 mg
- Two ongoing studies of the mechanism of action

Clinical pharmacology studies were discussed in Section 6 of the NDA, and all reported adverse events were included in the summary tables in Section 7 of the sponsor's integrated summary.

2) Two WHO/HRP-sponsored studies of levonorgestrel for emergency contraception, using Postinor (levonorgestrel 0.75 mg), manufactured by

- WHO/HRP 1998 – Study 92908
- Ho and Kwan – WHO/HRP Study 81107

3) Three WHO/HRP-sponsored trials of routine postcoital contraception with the levonorgestrel 0.75 mg formulation manufactures by

- 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 contraceptive use, with a variety of regimens, doses, and formulations. Early trials in Latin America (1970-1975) used formulations of levonorgestrel produced by Schering. In late 1970s and 1980s, provided Postinor (levonorgestrel 0.75 mg) for company-sponsored or partially-supported studies in Eastern Europe and Thailand.

5) Other sources of safety data such as a literature search, and post-marketing spontaneous event reports.

The types of safety data reported for each study are indicated in the Sponsor's table below:

Types of Safety Data for Each Study

Study	Adverse Event	SAE	Adverse Withdrawal	CRF	Lab Data	Vital Signs	Pregnancy Outcome
WCC-PK001	X	X	X	X	X	X	
He 1990							
Durand	X						
WHO/HRP 91902							
WHO/HRP 92908	X	X		X			X
Ho and Kwan	X					BP, P	X
WHO/HRP 82906	X		X	X			
He 1991	X		X				X
WHO/HRP 87908	X		X	X			
Farkas,1978	X						
Seregély	X		X				X
Borsos	X					BP, Wt	X
Kovács 1979	X						
Farkas 1982					Histology		
Husvéth	X						X
Kovács 1983	X				X		X
Verö			X				
Kiss	X						
Tatár	X						X
Karsay	X				X	BP	
Polgár	X		X				
Huber	X						
Domány	X				X	BP	
Chernev	X						
Szczurowicz	X						
Nirapathpongporn	X						

Study	Adverse Event	SAE	Adverse Withdrawal	CRF	Lab Data	Vital Signs	Pregnancy Outcome
Czekanowski	X						
Klawe	X						X
Canzler	X				X	BP	
Orley	X					BP, Wt	
Sas	X						
Echeverry	X					BP	
Kesserü	X	X	X				
Moggia	X		X		X		X
Hurtado	X						
Larrañaga	X		X				
Hoffmann	X						

SAE= Serious Adverse Event, CRF= Case Report Form, BP= Blood Pressure, P= Pulse, Wt= Weight

3.2 Summary of Related Levonorgestrel Trials:

A relative large body of older foreign studies of levonorgestrel taken alone after coitus for routine or occasional postcoital contraception are summarized in the sponsor's table below.

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.

STUDY	REGIMEN
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

Several of the studies listed above were carried out in South America and supported by Schering A.G. on doses ranging from 0.15 mg to 1.0 mg levonorgestrel. The majority of the studies used the levonorgestrel 0.75 mg tablet manufactured by

It is difficult to compare results between these trials because of differences in underlying risk of pregnancy and in lengths of follow-up, as well as patient populations and dosing regimens. Nonetheless, these early studies of different dose levels appear to have influenced decision to develop a 0.75 mg levonorgestrel tablet in the late 1970s and influenced WHO/HRP to use this tablet in several studies of levonorgestrel for routine postcoital contraception, and more recently in the two controlled studies on emergency contraception for this NDA.

Reviewer's comment: The 0.75 mg levonorgestrel dose appears reasonable based on the various studies carried out during the past 25 years. Lower doses have been used, but were often administered within 1-8 hours of intercourse and showed more disruption of the women's menstrual cycles.

The authors of these studies provide few details on their procedures for detection of pregnancies or for following up with women who failed to keep appointments. It is likely that some pregnancies were missed. Efficacy results were presented by several of the investigators in terms of the Pearl index, which ranged from 0 to 21.1 pregnancies per 100 woman-years. The Pearl index is calculated as the number of unintended pregnancies divided by the number of woman-years of exposure to risk of pregnancy. The studies of different doses of levonorgestrel suggest greater efficacy (lower Pearl indices) might be at higher doses. The Pearl index, however, has an intrinsic flaw. Because fertile women are likely to become pregnant earlier and thus drop out of the study, this statistic tends to decrease with increasing duration of follow-up. The studies with the shortest follow-up indeed tended to report the highest Pearl indices. Despite these problems, however, the estimated Pearl index among women using no contraception (approximately 85 pregnancies per 100 woman-years) is much higher than that observed in any of these above studies using levonorgestrel alone for contraception. Therefore, these results generally support that postcoital use of levonorgestrel appears to be effective. The findings are only marginally relevant, however, to the efficacy of the proposed two-dose levonorgestrel regimen for emergency contraception because the dosing regimens were so different.

3.3 Comparison of the Phase III Ho and Kwan and WHO Pivotal Controlled Trials

Two well-controlled studies have evaluated a two-dose regimen of levonorgestrel 0.75 mg tablets specifically for emergency contraception. Both were double-blind randomized trials comparing the levonorgestrel regimen of emergency contraception to the standard Yuzpe regimen. These two trials are the focus of this NDA review.

The pivotal study (WHO/HRP 1998 – Study 92908) for this NDA was designed, monitored, and analyzed by the United Nations/WHO/World Bank Special Programme of Research, Development and Research

Training in Human Reproduction (WHO/HRP). It was conducted between 1995 and 1997 at 21 clinical sites in 14 countries on five continents.

At WCC's request, WHO/HRP provided the raw data to Family Health International (FHI), a nonprofit research organization specializing in contraceptive research and development. The Study Report on the Pivotal Study included in this submission was prepared by FHI. They used the results of their own analyses and WHO/HRP's Report of Final Analysis, as well as information on the study published in *Lancet*, in August of 1998.

The Ho and Kwan study was conducted at the Family Planning Association of Hong Kong in ~1992. According to the study's principal investigators, the original data forms and data listings no longer exist. The information provided below was taken solely from the report published in 1993 in *Human Reproduction*. This study used an open-label design. Interim analyses were to be performed after the first 200 subjects were recruited and again after each additional 100. If the failure rate of levonorgestrel group was more than 5 times the Yuzpe group, the study was to be stopped. Interim analyses were performed per the protocol.

The regimens evaluated in the two studies are described in the table below. The Yuzpe and levonorgestrel regimens were identical in the two studies, with two exceptions:

- The Pivotal Study (WHO/HRP 1998 – Study 92908) allowed women to initiate treatment up to 72 hours after intercourse, whereas Ho and Kwan limited initiation of treatment up to 48 hours after intercourse.
- In the Pivotal Study 92908, women in both groups were provided with a replacement dose of drug to take if vomiting occurred within four hours after either required dose. The Ho and Kwan study did not provide a third dose in case of vomiting.

Regimens Evaluated in the Two Controlled, Double-Blind Phase III Trials of Levonorgestrel for Emergency Contraception

	Pivotal Study (WHO/HRP 1998 – Study 92908)	Ho and Kwan (1993)
Levonorgestrel	0.75 mg levonorgestrel within 72 hours after intercourse, followed by the same dose 12 hours later; a third dose taken if vomiting occurred within four hours after either required dose	0.75 mg levonorgestrel within 48 hours after intercourse, followed by the same dose 12 hours later; no third dose available
Yuzpe	0.1 mg ethinyl estradiol and 0.5 mg levonorgestrel within 72 hours after intercourse, followed by the same dose 12 hours later; a third dose was to be taken if vomiting occurred within four hours after either required dose	0.1 mg ethinyl estradiol and 0.5 mg levonorgestrel within 48 hours after intercourse, followed by the same dose 12 hours later; no third dose available

Efficacy results from the Ho and Kwan study showed higher than the expected 2% rate of pregnancy in both arms. Discussion about this finding follows later in this review. The sponsor's table below shows a direct comparison of the efficacy results of the two large controlled trials. No difference was observed between the pregnancy prevented fractions in the two treatment arms (60% vs. 59%) in the Ho and Kwan study.

Efficacy Results, Efficacy Population

	WHO 92908	Ho and Kwan
Levonorgestrel		
Number of women	976	410
Number of pregnancies	11	12
Pregnancy rate (%)	1.1% (0.6, 2.0)	2.9%
Number of observed/expected pregnancies †	11/76.3	8/19.8*
Prevented fraction (%)	86 (74, 93)	60*
Yuzpe		
Number of women	979	424
Number of pregnancies	31	15
Pregnancy rate %, (95% CI)	3.2 (2.2, 4.5)	3.5%
Number of observed/expected pregnancies †	31/74.2	9/22.0*
Prevented fraction %, (95% CI)	58 (41, 72)	59*

*Among 331 women (levonorgestrel group) and 341 women (Yuzpe group) who had reliable menstrual dates. Women who had additional acts of intercourse were to have been excluded.
†Expected pregnancies calculated using Dixon's expected probabilities of pregnancy by cycle day.

Baseline characteristics in the two controlled trials were very similar except to note the obvious difference in ethnic category because 100% of the subjects in Ho and Kwan were Chinese. In the Pivotal Study just under 50% of enrollees started treatment within 24 hours of intercourse, whereas almost two-thirds did in the Ho and Kwan study. In both studies, analyses stratified by interval between intercourse and start of treatment showed that shorter intervals were associated with lower pregnancy rates in both treatment groups. In both studies, weight was not significantly associated with risk of pregnancy, but women who had additional acts of intercourse had more than twice the risk of pregnancy than women who did not.

4.0 WHO Pivotal Study 92908

4.1 Objective/Rationale

The objectives of this multicenter study were the following:

1. To confirm the findings of Ho and Kwan that two doses of levonorgestrel 0.75 mg given 12 hours apart for emergency contraception have the same effectiveness as, but fewer side effects than the Yuzpe regimen.

2. To assess whether the same effectiveness could be achieved if the permissible 48-hour delay between intercourse and the start of treatment were extended to 72 hours.

4.2 Overall Design and Plan

This prospective, double blind, randomized, multicenter trial compared two treatment regimens of emergency contraception: levonorgestrel 0.75 mg *versus* 0.1 mg ethinyl estradiol combined with 0.5 mg levonorgestrel, known as the Yuzpe regimen. One dose of each treatment was given orally 12 hours apart in women presenting within 72 hours after an act of unprotected intercourse. Women in both treatment groups were given a third dose of study medication to take if vomiting occurred within four hours of either dose.

According to the original plan for the study, 100 women at each of 19 centers presenting for emergency contraception who satisfied the criteria for subject selection and who were willing to participate were to be recruited after informed consent had been obtained. Subjects were to be allocated randomly to one of the two treatment regimens. They were to be given diary cards to record vaginal spotting and bleeding, adverse events, any further acts of intercourse, use of additional contraception and the time of administration of study drugs. The actual study used 21 centers enrolling from 42 to 200 women as shown in the table below.

Number of Subjects per Center per Treatment Group

Center	Center No.	Levonorgestrel	Yuzpe	All Groups
Stockholm, Sweden	1	49	49	98
New Delhi, India	6	50	50	100
Szeged, Hungary	8	39	39	78
Ljubljana, Slovenia	9	49	50	99
Pittsburgh, USA	78	36	38	74
Quebec, Canada	170	33	30	63
Lagos, Nigeria	302	50	50	100
Manchester, England	789	29	29	58
Panama, Panama	1162	30	30	60
Jos, Nigeria	1195	50	50	100
Shanghai, China	1326	50	50	100
Beijing, China	1378	50	50	100
Nanjing, China	1423	100	100	200
Tbilisi, Georgia	1489	50	50	100
Tianjin, China	1539	50	50	100
Sagamu, Nigeria	1757	75	75	150
Northbridge, Australia	1983	39	37	76
Ulaanbaatar, Mongolia	1996	75	75	150
Auckland, New Zealand	2008	22	20	42
Christchurch, New Zealand	2009	25	25	50
Wellington, New Zealand	2010	50	50	100
TOTAL		1001	997	1998

A follow-up appointment was scheduled seven days after the expected onset of the next menstruation. If no bleeding had occurred by that time, a pregnancy test (hCG) was to be performed. If bleeding had occurred, pregnancy was presumed to be ruled out clinically.

A detailed analysis plan was not provided in the original protocol. FHI states that they prepared the revised analytical plan in February 1998, before unblinding the data.

In accordance with usual practice in the analysis of results from studies in emergency contraception, failure rates in the two groups were to be compared not only in terms of raw pregnancy rates (number of pregnancies per 100 women treated), but also in terms of standardized rates that take into account the number of pregnancies that would have been expected if no treatment had been given. The number of expected pregnancies would be calculated from the estimates of the probability of pregnancy on different days of the cycle (using the Dixon and Wilcox probabilities).

Primary safety outcomes were defined as the incidence of side effects, expressed as the percentage of women reporting a side effect within seven days of treatment among the total number of participants in the Safety Population (the same as the sponsor's Efficacy Population). Other safety outcomes to be analyzed were the percentage of subjects needing an extra dose, the amount and duration of bleeding at next menstruation and the delay in onset of menses.

4.3 Study Population

Women in need of emergency contraception were selected from their respective clinic populations. Some women presented to the centers in response to local announcements about the study. All were above the age of consent within their own countries. After they signed a consent form, eligible subjects were randomized to one of two treatment groups. No incentives were provided.

4.4 Inclusion and Exclusion Criteria

Inclusion criteria: women admitted to the study were required to fulfill all of the following:

- good general health
- able to give informed consent
- requesting emergency contraception within 72 hours after unprotected coitus
- with only one act of unprotected coitus during the current menstrual cycle
- willing to abstain from further acts of unprotected intercourse during that cycle or to use a condom or diaphragm if that were not possible
- have a history of regular spontaneous cycles (24-42 days)
- women who recently discontinued hormonal contraception or who had a recent abortion or delivery should have had at least one spontaneous cycle of normal length before the current cycle
- available for follow-up and living in the study area for at least the next six weeks
- willing and able to participate after the study had been explained

Reviewer's comment: The above criteria do not include any age limitation, and it is of interest that two (5%) of the documented failures were in women 40 and 43 years old (both were from the Beijing, China center). The criteria of at least one spontaneous period since recent OC use, abortion or delivery does not assure a return to ovulation (and hence these women might not have been at risk of pregnancy); the "regular cycle" window of 24-42 days is liberal, especially at the upper end.

Exclusion criteria: women were not to be recruited if any of the following applied:

- currently pregnant or breastfeeding
- use of hormonal methods of contraception during the current cycle
- unprotected intercourse due to failure of the barrier method (displacement of diaphragm; slippage or leakage of condom) when used together with spermicide
- unsure about the date of the last menstrual period
- a contraindication to the use of exogenous steroids

Reviewer's comment: Although the first four criteria do not affect the safety of the subjects in the trial, they could confound the analysis of the primary efficacy endpoint, pregnancy. It is particularly concerning that pregnancy was not routinely ruled out at baseline with a mandatory negative pregnancy test. A baseline urine pregnancy test was done in 1013 (50.7%) of the total 1998 women; this testing was evenly distributed between the two treatment groups. Only 61 women (3%) had serum pregnancy testing done at baseline; 58 of these subjects represented complete enrollment at a sole site (Panama). Thus, 46.3% of the total enrolled patients had no laboratory determination of pregnancy at baseline.

The purpose of the exclusion of women who had a contraindication to exogenous steroids was to exclude women who should not receive the Yuzpe regimen containing the estrogen ethinyl estradiol. Individual sites apparently interpreted this exclusion statement on their own without clear instructions regarding what constituted a "contraindication to the use of exogenous steriods."

4.5 Visits and Treatment Period

There were only two scheduled visits in this study. Women who met the above inclusion/exclusion criteria were enrolled in the study at the time of the screening visit (Visit 1). At each site, subjects were assigned to one of two treatment groups according to a computer-generated randomization schedule provided by the Statistics and Data Processing Unit at WHO/HRP. Each center received assignments by random permuted blocks with a fixed block size of ten. Participants were given general instructions, a diary card to complete daily, and a return appointment (Visit 2) for approximately one week after the first day of their next expected menses. A Visit 3 was scheduled only if the pregnancy status of the woman was uncertain at Visit 2.

Time and Events

	Visit 1 Enrollment				Visit 2 Follow-up 1	Visit 3* Follow-up 2
	Day 1	12 Hours later	Day 2	Day 3-7	1 week after next expected menses	7 Days After Visit 2
Informed Consent	X					
Enrollment	X					
Randomization	X					
Medical History	X					
Physical Examination	X				X*	
Pregnancy Test	X				X*	X*
Study Medication	X	X				
Diary Card		X	X	X		
Review Diary Adverse events					X	X

* If needed to resolve pregnancy status.

Study participants in the group assigned to levonorgestrel received two doses, each consisting of one 0.75 mg tablet of levonorgestrel plus one placebo tablet, orally 12 hours apart beginning within 72 hours of an unprotected act of intercourse. Study participants in the Yuzpe group received two doses of two combined tablets of ethinyl estradiol 0.05 mg/levonorgestrel 0.25 mg orally 12 hours apart beginning within 72 hours of an act of unprotected intercourse. By protocol, the first dose was swallowed in the presence of a staff member who recorded the date and time. The second dose was taken after 12 hours.

Reviewer's comment: Women in this controlled trial usually received their first dose in the clinic under direct supervision. In contrast, women prescribed Plan B for potential emergency use may not be as compliant with dosing instructions. Labeling should clearly emphasize the need to begin dosing as soon as possible after unprotected intercourse. Some women delayed their first dose so that the second dose, taken 12 hours later, would come at a more convenient time (e.g., at 7 am instead of 3 am). Only seven out of 1955 women in the Efficacy Population did not take the second dose within 24 hours of the first.

In order to exclude that the woman was pregnant already, it was recommended that centers carry out at least one of the following: pelvic exam, urine pregnancy test, ultrasound exam, blood (serum) hCG assay, or collection of a blood sample for storage to be analyzed if the woman was found to be pregnant at follow-up.

Reviewer's comment: Refer to the MO Table below for data on pregnancy testing at the two visits. In general, 14 of 21 centers did some urine pregnancy testing at the entry (baseline) visit V1; limited serum samples (17%) were collected for future use if indicated. Nine of the women who were determined to be pregnant at the follow-up visit (V2), however, did NOT have either a blood or urine hCG result from their entry visit. This presents the possibility that these women were pregnant before enrolling in the study. The sponsor determined, in fact, that four women were pregnant at the time of the entry visit V1.

The following table, compiled by the medical officer, lists all the urine and blood (serum) pregnancy testing that was performed at each center and both the routine study visits.

MO Table: Pregnancy Testing of Subjects
Treatment Groups: L=levonorgestrel and Y=Yuzpe

Center	# subjects	V1 Urine	V1 Urine %	V1 Blood Draw	V1 Serum Tested	V2 Urine	V2 Blood Tested	# of IUP
Stockholm	98	49L 49Y	100	0		6L 4Y	0	1
New Delhi	100	8L 10Y	18	33L 36Y	0	2L 3Y	0	2
Szeged	78	28L 29Y	73	0	0	0	0	0
Ljubljana	99	0	0	0	0	4L 2Y	0	0
Pittsburgh	74	34L 38Y	97	36L 38Y	0	0L 3Y	0	3*
Quebec	63	33L 30Y	100	0	0	3L 1Y	1L 1Y	0
Lagos	100	26L 31Y	57	9L 04Y	0	1L 1Y	0	1
Manchester	58	0	0	1L 02Y	0	2L 3Y	0L 1Y	3*
Panama[a]	60	1L 1Y	3	29L 30Y	28L 30Y	2L 2Y	0	3*
Jos, Nigeria	100	0L 1Y	1	16L 14Y	0	0	0	0
Shanghai[b]	100	25L 25Y	50	0	0	2L 5Y	0	4*
Beijing	100	0	0	39L 40Y	0	1L 0Y	1L 0Y	6*
Nanjing	200	99L 100Y	100	1L 01Y	1L 0Y	3L 4Y	0	6
Tbilisi	100	0	0	0	0	0L 1Y	0	0
Tianjin	100	50L 49Y	99	0L 1Y	0	1L 1Y	0	3
Sagamu	150	1L 1Y	1	0	0	1L 5Y	0	1
Northbridge	76	39L 37Y	100	0	0	27L 25Y	0	1
Ulaanbaatar	150	32L 33Y	43	6L 5Y	0L 1Y	0	0	0
Auckland	42	6L 6Y	26	0	0	10L 6Y	0	3*
Christchurch	50	23L 23Y	92	0	0L 1Y	4L 5Y	0	2*
Wellington	100	49L 47Y	96	0	0	5L 5Y	0	3
TOTAL	1998	503L/510Y	50.7%	170L/171Y	29L/32Y	74L/76Y	2L/2Y	42

* Centers with 4% or higher pregnancy rates
[a]Panama was the only center to screen enrollees with serum pregnancy testing
[b]Shanghai: the first 50 women had V1 urine testing, and then it was discontinued

Reviewer's comments: The following points can be concluded based on the above table:

1. **Although not performed routinely, pregnancy testing at baseline was evenly distributed between the Plan B (L) and the Yuzpe (Y) treatment arms, accounting for approximately 50% of the total enrollment in the study.**
2. **A relatively small number of centers accounted for the majority of baseline urine pregnancy tests: 8 of 21 centers performed baseline urine testing in greater than 90% of their enrollees.**
3. **Overall, 17% (341 of 1998) of the subjects, evenly distributed between the two treatment arms, had blood drawn at baseline. These samples were saved for later analysis, but NOT used for pregnancy testing. According the sponsor's line listings, four patients (3 Yuzpe, 1 Plan B) were actually pregnant at the time of study enrollment and thus were not true treatment failures. Ten**

of the patients (see the MO listing of pregnant subjects in the Appendix) who were considered treatment failures at Visit 2, however, had no baseline laboratory evaluation to rule out pregnancy.

4. Only one site, Panama, performed routine serum pregnancy testing at baseline. Interestingly, three of the 4 patients pregnant at the time of study enrollment who nonetheless completed the study, were from Panama. If all sites had performed rigorous baseline pregnancy testing, the assessment of true treatment failures would have been more accurate.
5. Only 7.5% of enrolled subjects (74-76 of 1998—again evenly distributed between treatment arms) had urine pregnancy testing performed at follow-up Visit 2. Only 4 subjects had serum pregnancy testing at Visit 2. Thus, the large majority of detected pregnancies in this trial were based on clinical menstrual histories.
6. Despite the fact that only 54% of subjects had either urine or serum pregnancy testing at baseline, and only 7.5% had urine pregnancy testing at Visit 2 follow-up, it is reassuring to note that all test results were evenly randomized between the two study treatment arms.

The second visit collected data from the diary card concerning AEs, further acts of intercourse and contraception, vaginal spotting or bleeding, other complaints, and time of second dose of drug. In case the expected menstrual bleeding had not started by the follow-up visit, hCG (in blood or urine) was determined. If the hCG assay was negative, a further follow-up visit one week later was scheduled. If the assay was positive, an appropriate follow-up visit for further care was made.

Reviewer's comment: The lack of hCG pregnancy testing at baseline and especially at the follow-up visit V2 is a major flaw in the study design. There were no guidelines on interpreting the "menstrual bleeding" pattern that was recorded by individual participants. The assumption was that any bleeding that followed the two doses of study drug was considered to be a menstrual period and, therefore, an hCG assay was NOT routinely performed at the second visit. It is possible (especially if the bleeding was not "similar" to the usual pattern or was more than 4 days early or late) that some of these women were, in fact, pregnant and aborting or threatening to abort. The protocol did not call for an hCG assay on all participants; if performed, there would have been more accurate data on the true pregnancy rates following the two treatments. A detailed analysis by the MO of all women in the Pivotal Study who had "abnormal" follow-up menses can be found on page 26 of this MOR.

4.6 Evaluation Criteria

The primary outcome of the trial was the efficacy of the treatment in preventing pregnancy. All enrolled participants who provided information on pregnancy status at discontinuation were included in the primary analyses. The following two measures of efficacy were calculated for each group or subgroup in the Pivotal Study: pregnancy rate and the "prevented fraction" (the proportion of expected pregnancies prevented by the treatment).

4.7 Withdrawal, Lost to Follow-up, and Compliance

Women had the right to withdraw from the study at any time. The protocol did not specify criteria for discontinuation of subjects. In this Pivotal Study, with a two dose treatment for a one-time event and only one follow-up visit, withdrawal and lost to follow-up were considered the same event. The final pregnancy status was unknown in only 43 (2.2%) of the enrolled women, 25 of whom received PLAN B™ and 18 of whom received the Yuzpe regimen. Thus, the "Efficacy Population" included all but 43 of the total number of enrolled subjects.

According to the protocol, however, subjects could be further excluded from the "Perfect Use Population" analysis if one or more of the following criteria applied:

- the presence of vomiting during treatment
- the regular use of prescription drugs during the course of the study

- the use of other drugs between the treatment and the follow-up visit(s)
- further acts of intercourse
- any violation of the study protocol
- lack of essential data from the subject's records making it impossible to judge treatment outcome

Thus, the "Perfect Use Population" was much smaller, including slightly more than half of the subjects enrolled in each treatment arm (Plan B 574/1001= 57%; Yuzpe 583/997= 58%).

4.8 Sponsor's Efficacy Analyses

Baseline Characteristics:

No differences in baseline characteristics were detected between groups in the primary efficacy analysis population in either the Pivotal Study or the Ho and Kwan study (see table below). In both studies, the average age was about 27 years, and many women had previously been pregnant. The ethnic background of the women in the two studies differed substantially due to the locations of the study centers on five continents. In both studies, about half of the participants requested emergency contraception because of failure to use any method during intercourse, and the rest requested it because of method failure (such as a ruptured condom). Distribution of the day of intercourse relative to ovulation was similar between groups within each study. In both studies, the distribution was skewed such that more women had intercourse before ovulation than after.

Baseline Characteristics of Women, Efficacy Population *

	Pivotal Study		Ho and Kwan	
	Levonorgestrel	Yuzpe	Levonorgestrel	Yuzpe
Mean age in years (SD)	27.3 (7.0)	27.2 (6.8)	27.0 (6.4)	26.6 (6.7)
Age, years n, (%)				
≤25	444 (45.5)	470 (48.1)		
26-35	387 (39.6)	367 (37.5)		
≥36	145 (4.9)	141 (14.4)		
Ethnic Category (n, %)				
White	211 (21.6)	214 (21.9)		
White Pacific	128 (13.1)	123 (12.6)		
Black	174 (17.8)	175 (17.9)		
Mixed	142 (14.6)	145 (14.8)		
Chinese	321 (32.9)	322 (32.9)	410 (100)	424 (100)
Mean cycle length in days (SD)	28.9 (2.4)	28.8 (2.5)	30.9 (6.7)	30.5 (4.5)
Previously pregnant n, (%)	633 (64.9)	619 (63.2)	171 (41.7)	179 (42.2)
Previous use of emergency contraception (%)	203 (20.8)	227 (23.2)		
Reason for requesting emergency contraception				
No method use (%)	549 (56.3)	545 (55.7)	(39.8)	(46.2)
Method failure	425 (43.5)	431 (44.0)	(46)	(50.2)

*Data missing for some characteristics in each study.

Reviewer's comment: There were 500 women enrolled at the four centers in China. The sponsor's ethnic numbers above include 321 + 322 = 643 Chinese, because they counted the 150 women from the Mongolian center as Chinese. Emergency contraception may have less efficacy in Chinese women; this issue is discussed later in this review.

In each study, the two groups were also similar in the timing of intercourse and treatment received. In the Pivotal Study, just under 50% started treatment within 24 hours after intercourse, whereas in the Ho and Kwan study, almost two-thirds did so. The Pivotal Study also evaluated potential associations between efficacy rate and several other factors: cycle day of intercourse, whether or not participant had additional acts of intercourse, reason for request for emergency contraception, body weight, and body mass index. In both treatment groups, women who had additional acts of intercourse had more than twice the risk of pregnancy than women who did not (p=0.003). However, none of the interactions between any of these factors and treatment group were statistically significant in the sponsor's analysis.

Stratified analysis by age showed no effect of age on the risk of pregnancy (p = 0.6), and no interaction between age and treatment group. Analysis stratified by interval between intercourse and treatment showed that shorter intervals were associated with lower pregnancy rates in both groups (p = 0.01), as seen in the sponsor table below.

Efficacy Results Stratified by Time Interval Between Intercourse and Treatment
Sponsor Efficacy Population

	Interval between intercourse and treatment		
	≤ 24 hours	25-48 hours	>48 hours
Pivotal Study (WHO/HRP Study 92908) Efficacy Population			
Levonorgestrel			
Pregnancy rate, % (95% CI)	0.4 (0.1, 1.6)	1.2 (0.3, 3.0)	2.7 (0.9, 6.1)
Prevented fraction, %	95 (81, 99)	85 (61, 96)	61 (9, 87)
Yuzpe			
Pregnancy rate, %	2.0 (0.9, 3.7)	4.1 (2.3, 6.6)	4.7 (1.9, 9.4)
Prevented fraction, %	77 (56, 89)	38 (0, 66)	38 (-28, 75)
Ho and Kwan			
Levonorgestrel			
Pregnancy rate, %	1.8	3.5	NA*
Yuzpe			
Pregnancy rate, %	1.4	4.6	NA*

*Not applicable, because all subjects were to take the first dose within 48 hours

Reviewer's comment: Higher pregnancy rates were clearly noted among women who delayed taking the treatment for two or three days after intercourse. This finding is biologically plausible: the longer the treatment is delayed, the greater the likelihood that pregnancy may become established. This result does differ from the result of the Trussell meta-analysis of nine published studies, which found no effect of interval between coitus and treatment. The reason for this discrepancy is not clear. Nevertheless, the labeling of the PLAN B™ product should be written to encourage women to start the treatment as soon as is reasonably possible after intercourse.

Population Definitions:

The sponsor defined four populations of enrolled participants as:

1. **Recruited Population** (1,998 women): All women enrolled
2. **Efficacy Population** (1,955 women): All participants in Population 1 above except those 43 women for whom final pregnancy status was unknown
3. **Eligible Population** (1,855 women): All participants in Population 2 above except those 100 women with the protocol violations listed in the table below:
4. **Perfect Use Population** (1,157 women): All participants in Population 3 above except those 698 women who used the treatment imperfectly, defined in the table below:

Sponsor and MO Comparison
Number of Women in Each Analysis Population, by Treatment Group

Population	Pivotal Study 92908		MO Evaluation	
	PLAN B™ N	Yuzpe N	PLAN B N	Yuzpe N
1. Recruited Population	1001	997	1001	997
2. Efficacy Population	976	979	975	975
Includes all in Population 1 except:				
Final pregnancy status unknown[a]	25	18	25	18
3. Eligible population	933	922	933	921
Includes all in Population 2 except:[b]				
Pregnant at admission	1	3		
Non-evaluable at admission[c]	0	0		
Pregnancy status unknown at admission	2	3	Much larger (46%) NO hCG done	Much larger (46%) NO hCG testing performed
Initiated treatment more than 72 hours after intercourse	3	2		
Menstrual cycle not 24-42 days	7	8	Not checked	Not checked
Hormonal contraceptive methods during cycle before enrollment	0	1	Not checked	Not checked
Used condom with spermicide at the intercourse act prompting request for emergency contraception	31	42		
4. Perfect use population	574	583	Not checked	Not checked
Includes all in Population 3 except:[b]				
Failed to take second dose of study drug within 24 hours after the first dose[e]	3	4		
Used drugs during the study that could affect efficacy	14	7		
Had intercourse between admission and the next menstrual period.[d]	351	334		

Reviewer comments:
[a] This more accurately should state: NO follow-up visit 2.
[b] Some women had more than one reason for exclusion.
[c] The medical officer found two pregnant women that were pregnant at baseline and not considered pregnant at baseline by the sponsor
[e] Protocol clearly states that the 2nd dose was to be taken 12 hr later. Altogether 86 women had a late second dose, but 70 of these women were from the Jos, Nigeria site.
[d] A confounder in this study because of method vs. user failure. Method (or perfect use) failure means that the medication failed to prevent pregnancy when taken correctly, according to instructions, in the trial. User failure means that the user is the primary reason (e.g., did not take the medication properly or had further unprotected intercourse during the trial) for the failure to prevent pregnancy. Of the sponsor's Eligible Population, 37% had intercourse after taking the emergency contraception treatment, thus creating the much smaller Perfect Use Population.

Of the 37 MO failures, 21 (57%) had intercourse after the baseline visit and before the next expected menstrual period. It is reassuring, however, that the overall pregnancy rates and pregnancy prevention fractions in the non-perfect use populations were almost identical to those in the Perfect Use Population.

Efficacy Population:

The sponsor's Efficacy Population was the primary efficacy analysis population. This population was basically the ITT (intent-to-treat) population minus the 43 women who were lost to follow-up. Results reported were calculated using the Efficacy Population unless otherwise specified. Baseline characteristics of participants were summarized for this population. Secondary efficacy analyses were performed using Populations 3 and 4. WCC's proposed labeling made efficacy claims based on the Perfect Use Population.

Reviewer's comment: The only difference between the sponsor's Efficacy Population and the MO "Evaluable Population" is that the MO eliminated five additional women from the sponsor's Efficacy Population. The five women were determined by the MO to be either pregnant at baseline (subjects 078-26, 1162-03, and 1162-44) or not pregnant due to the unprotected intercourse for which they took the study treatment (subjects 06-96 and 789-36). Thus, the total sponsor Efficacy Population (976+979 women) and the MO Evaluable Population (975+975) differ somewhat.

The lower one-sided 95% confidence bound around the ratio of the odds of pregnancy in the Yuzpe group to the odds in the levonorgestrel group was 1.53. The Breslow-Day test of homogeneity across centers showed no difference in odds ratios between centers. Since the lower confidence bound was greater than 0.5, levonorgestrel was deemed to be as effective as the Yuzpe regimen. The fact that this bound was greater than 1 was considered by the sponsor evidence that levonorgestrel was statistically more effective than the Yuzpe regimen.

A total of 42 pregnancies occurred in the sponsor's Efficacy Population: 31 in the Yuzpe group and 11 in the levonorgestrel group, which gives crude failure rates of 3.2% (95% CI 2.2-4.5%) and 1.1% (95% CI 0.06-2.0%) respectively, and a crude relative risk (RR) of 2.81 (95% CI 1.4-5.6).

A comparison of the pregnancy rates and relative risk (RR) in the sponsor's Efficacy Population and the MO's Evaluable Population is seen in the following table:

Comparison of Sponsor and MO Pregnancy Rates and Relative Risk

Sponsor Efficacy Population			Crude rates and relative risk					
Group	No. of subjects							
		Observed Pregnancies	Rate (%)	95% CI		RR	95% CI	
				L	U		L	U
Levonorgestrel	976	11	1.1	0.6	2.0	1		
Yuzpe	979	31	3.2	2.2	4.5	2.81	1.42	5.56

MO (Medical Officer) Evaluable Population			Crude rates and relative risk					
Group	No. of subjects							
		Observed Pregnancies	Rate (%)	95% CI		RR	95% CI	
				L	U		L	U
Levonorgestrel	975	10	1.0	0.5	1.9	1		
Yuzpe	975	27	2.8	1.8	4.0	2.7	1.31	5.52

Reviewer comment: In the sponsor's Efficacy Population the medical officer eliminated 5 pregnant women as non-evaluable for the detailed reasons listed below. Thus, the sponsor had 42 pregnant subjects and the MO had only 37. The complete MO listing and analysis of the 42 women who were pregnant during the pivotal study is found in a table format at the end of this review in the Appendix.

1. **New Delhi patient #06-96: This woman started her menstrual period on 2/26, had unprotected intercourse on 3/3, 13 days before expected ovulation, and the sonogram showed a 3/19 conception date. She had four episodes of intercourse after she took the study medication. The likelihood that she became pregnant as a result of a failure of the study medication is virtually zero. Thus, she should not be counted as a study failure.**
2. **Pittsburgh patient #78-26: had a positive serum hCG test at the baseline admission visit.**
3. **Manchester patient 789-36: had unprotected intercourse 10 days before expected ovulation, took the first dose at 140 hours (almost 6 full days) after intercourse, and had two further acts of intercourse later in the same cycle. No baseline labs were done and no sonogram was performed confirming the probable date of conception. Thus, she should not be counted as a study failure.**
4. **Panama patient #1162-03: had a positive serum hCG test at the baseline admission visit.**
5. **Panama patient #1162-44: had a positive serum hCG test at baseline admission visit.**

Also of note is that fact that the sponsor considered Panama patient #28 as pregnant at the baseline visit because the pregnancy test was supposedly positive, and the investigator thought that conception occurred on 10/22 by a later sonogram evaluation. After careful review of the CRF, the MO determined that the subject's last menstrual period started 10/22, that unprotected intercourse on 11/7 occurred at the time of ovulation, and the later sonogram confirmed conception on approximately 11/4. The serum hCG drawn at the baseline visit on 11/8 was not performed. Thus, the MO considered this as an evaluable patient who became pregnant at the time of the entry visit and who should be counted as a study treatment failure.

The expected number of pregnancies was 74 and 76 by the Dixon method in the Yuzpe and in the levonorgestrel groups respectively. The expected number of pregnancies divided by the actual number of pregnancies is called the "prevention fration." Thus, the prevention fractions were 58% (95% CI 41-72%) and 86% (95% CI 74-93%), respectively. When using Wilcox-r probabilities, the results were almost identical.

A comparison of the prevention fraction of the sponsor's Efficacy Population and the MO's evaluable population is seen in the following table:

Comparison of Prevention Fractions

Sponsor Efficacy Population					
Treatment Group	No. of Subjects	No. of Pregnancies	# Expected Pregnancies	Prevention Fraction (%)	95% CI
Plan B	976	11	76	86	(74, 93)
Yuzpe	979	31	74	58	(41, 72)
Medical Officer Evaluable Population					
Plan B	975	10	76	87	(77, 94)
Yuzpe	975	27	74	64	(52, 74)

Reviewer's Comment: In the MO Evaluable Population there were a total of 27 pregnancies in the Yuzpe group and 10 in the levonorgestrel group. Using the Dixon method to calculate the sponsor's expected number of pregnancies in the sponsor's Efficacy Population, the MO prevented fractions were 47/74= 63.5% (95% CI 52,74) and 66/76= 86.8% (95% CI 77,94) respectively with a ratio of 100-63.5/100-86.8 = 36.5/13.2 = 2.77. The MO did not attempt to calculate additional sets of values for the Eligible and Perfect Use Populations that are discussed below.

Eligible Population:

Among the 1,855 women in the sponsor's Eligible Population (women without protocol violations listed in the table on page 21), 23 pregnancies occurred in the Yuzpe group and 8 in the levonorgestrel group. The pregnancy rates in the Yuzpe and levonorgestrel groups in this population were 2.5 and 0.9% respectively, and the relative risk was 2.9 with a 95% confidence interval (1.3, 6.5).

Reviewer's comment: Discussions with the FDA statistician David Hoberman have pointed out that the shortcomings of the sponsor's assertion that superiority was clearly demonstrated include:

- **the small overall number of pregnancies**
- **the surrogate endpoint of vaginal bleeding (as opposed to urine or serum pregnancy testing)**
- **the fact that this was a single trial**
- **if there were as few as five missed pregnancies in the Plan B group of the MO evaluable population, then the difference in the two treatment groups would not be statistically significant.**
- **the Ho and Kwan study demonstrated no significant difference in the pregnancy rates**

Perfect Use Population:

Among the sponsor's 1,157 women in the Perfect Use Population, 11 pregnancies were noted in the Yuzpe group and 5 in the levonorgestrel group. This gives crude failure rates of 1.9 and 0.9% (95% CI 0.3-2.0%) respectively, and a crude RR of 2.2 (95% CI 0.8, 6.2). In the Perfect Use Population, 89% of expected pregnancies were prevented by levonorgestrel using the Dixon and Wilcox methods to estimate expected pregnancies. For the Yuzpe group, 76% (Dixon method) or 74% (Wilcox method) were prevented.

Reviewer's comment: Using the sponsor's same analysis seen above for the Eligible Population, the pregnancy rates in the Yuzpe and levonorgestrel groups in this Perfect Use population were 1.9 and 0.9% respectively. The relative risk was 2.2. The 95% confidence limit around the relative risk (0.8, 6.2) did not exclude 1, indicating that in this Perfect Use Population, the levonorgestrel regimen was <u>not</u> statistically more effective than the Yuzpe regimen.

Chinese Population:

The following MO table takes collective data from the Chinese and non-Chinese subjects in the WHO pivotal study and separates it to the two treatment arms. The sponsor and MO difference in the number of enrolled subjects is explained in the reviewer's comment. Data from the Ho and Kwan study (100% of subjects were Chinese) is also listed for comparison and comment.

Comparison of Chinese and Non-Chinese Pregnancy Rates

Sponsor Efficacy Population- Pivotal Study 92908				
Ethnic group	Treatment	# Subjects	# Pregnancies	Pregnancy Rate %
Chinese	Levonorgestrel	321	5	1.6%
Non-Chinese		655	6	0.9%
Chinese	Yuzpe	322	14	4.3%
Non-Chinese		657	17	2.6%
MO Evaluable Population- Pivotal Study 92908				
Chinese	Levonorgestrel	246	5	2.0%
Non-Chinese		730	5	0.7%
Chinese	Yuzpe	247	14	5.7%
Non-Chinese		732	13	1.8%
Efficacy Population- Ho and Kwan Study				
Chinese (100%)	Levonorgestrel	410	12	2.9%
	Yuzpe	424	15	3.5%

Reviewer's comment: There were 500 women enrolled at the 4 centers in China; these 4 centers contributed 5 of the 10 levonorgestrel failures and 14 of the 27 Yuzpe failures. Thus, 50% of the total failures in the study came from 25% of the overall Efficacy Population (493/1955 = 25%). The sponsor's ethnic numbers differ form the MO's because the sponsor counted the women from the Mongolian center (where there were no failures) as Chinese while the MO did not. In the pivotal study, the pregnancy rates were consistently higher in the Chinese subjects compared to the non-Chinese. Also of note is the fact that the pregnancy rates in the Efficacy Population of the exclusively Chinese population in the Ho and Kwan study compared to the Pivotal Study were higher in both the levonorgestrel arm (2.9% vs. 1.1%) and in the Yuzpe arm (3.5% vs. 3.2%). These facts suggest that both Plan B and Yuzpe methods of emergency contraception have less efficacy in Chinese women.

Second and Third Dose by Protocol:

The regimen used in the Pivotal Study permitted a third dose of levonorgestrel or the Yuzpe regimen; women were instructed to take a third dose in case of vomiting within 4 hours of taking either the first or second dose. This third dose is not included in the sponsor's proposed label, since it was used by less than 5% of the women in the levonorgestrel group. A reanalysis by the sponsor of the Pivotal Study under the conservative assumption that the trial regimen would have been entirely ineffective had the extra dose not been available to women who took it, showed that the extra dose did not contribute materially to the efficacy of the regimen. With the third dose, the regimen prevented 86% of expected pregnancies in the

Efficacy Population, and without it, it would have prevented 82%. This finding reflects the fact that vomiting is uncommon in women using the PLAN B™ regimen, and consequently only 4.8% of study participants in the levonorgestrel arm took the third dose for any reason. Without evidence that the extra dose improves efficacy, and given the fact that inclusion of the extra dose complicates the regimen, and may result in increased potential for misuse, the sponsor recommends that this extra dose not be included in the proposed commercial product nor in proposed labeling.

Reviewer's comment: The MO agrees with not providing an extra dose of Plan B for the proposed commercial product. The label should advise, however, that consultation with a healthcare provider may be considered in cases of vomiting that occur within one (1) hour of taking either dose of PLAN B™.

According to the study protocol, the second dose of study treatment was to be administered 12 hours after the first dose. A late second dose was taken by 86 (4.4%) of the 1,998 women in the study. Seventy of these 86 women were at the Jos, Nigeria site (enrollment of 99) and had intervals between the two doses of greater than 18 hours. The other 16 women were from 12 other sites, so a late second dose was very uncommon except at the Jos, Nigeria site.

Reviewer's comment: Of importance, is the fact that there were <u>no failures</u> among any of the 86 women who took their second dose ≥ 6 hours later than instructed. All 37 failures (pregnancies) in the MO evaluable group took their second dose 11-12 hours after the first dose; 4 of the failures (3 Yuzpe and 1 levonorgestrel) also took a third dose of study treatment.

4.9 Sponsor Safety Analysis and Reviewer's Comments

All 1,956 subjects in the Safety Population (same as the Efficacy Population) who reported safety data were included in the sponsor's safety analyses. Only 4.8% of enrolled women in the levonorgestrel group received a third dose to compensate for vomiting, resulting in a potential total dose of 2.25 mg. More women (9.1%) took a third dose of the Yuzpe regimen. Because of confounding, adverse events were not analyzed by total dose received, (*e.g.*, women only received the third dose after vomiting, so it is unknown whether a third dose could increase vomiting). No subject took a fourth dose of either treatment.

A checklist of adverse events and menstrual events was provided on the subject diary card. The checklist was completed daily for seven days after enrollment. The list included nausea, vomiting, headache, dizziness, fatigue, breast tenderness, lower abdominal pain, diarrhea, "other", and vaginal spotting or bleeding. Additional comments were written on the CRFs. WHO/HRP entered all medical text including the "other" adverse events into a database for coding medical text. The database was coded at FHI according to COSTART terms to group events by body system. Information about severity and seriousness of these adverse events was not collected. The recording was a simple yes/no for each AE.

Common Adverse Events (AEs):

The most common adverse events included nausea, menstrual changes, and non-specific complaints. Overall, fewer events occurred in the levonorgestrel group than in the Yuzpe group. A significantly lower percentage of women in the levonorgestrel group reported nausea, vomiting, dizziness, or fatigue compared to the Yuzpe group (see table below). Fewer women reported headache and lower abdominal pain in the levonorgestrel group.

Adverse Events in >1% of Women, by Body System

Body System/ Preferred Term	Levonorgestrel N=977 (%)	Yuzpe N=979 (%)
Body, Whole		
Abdominal pain	172 (17.6)	205 (20.9)
Fatigue*	165 (16.9)	279 (28.5)
Flu syndrome	10 (1.0)	9 (0.9)
Digestive		
Nausea*	226 (23.1)	494 (50.5)
Vomiting*	55 (5.6)	184 (18.8)
Diarrhea	49 (5.0)	64 (6.5)
Nervous		
Dizziness*	109 (11.2)	163 (16.6)
Headache	164 (16.8)	198 (20.2)
Urogenital		
Breast tenderness	105 (10.7)	118 (12.1)
Bleeding more	133 (13.8)	116 (12.2)
Vaginal hemorrhage	10 (1)	12 (1.2)

*Significantly lower in the Levonorgestrel group

Reviewer's comment: The data support the sponsor's claim that the incidence of nausea, vomiting, dizziness, and fatigue were significantly less (p-value <0.01) for women using levonorgestrel than for women receiving the Yuzpe regimen. This difference was undoubtedly due to the presence of estrogen (ethinyl estradiol) in the Yuzpe regimen. It is also supported by the fact that similar findings were confirmed in the earlier Ho and Kwan study comparing the identical two treatment arms.

Common Menstrual Events Following Treatment:

The mean duration of bleeding in the next menses was 4.7 days, the same in both the levonorgestrel and Yuzpe groups (SD 1.4). The percentages of women with an amount of bleeding less than normal, normal, and more than normal menses were almost identical in the two groups (p=0.590). Approximately 75% in both groups had an amount similar to normal menses, 12-13% had an amount more than normal menses, and 12% had bleeding less than normal. For both groups combined, 13% of women had a delay of more than 7 days beyond the anticipated onset of next menses; 14-15% had a delay of 3-7 days; 57% had menses return within 3 days of the expected day; and 15% had an onset 4-7 days earlier than expected (see table below).

Change in Timing of Next Menses

Sponsor Safety Population, excluding pregnant women

Timing of menses relative to expected date	Levonorgestrel N=966		Yuzpe N=949	
	N	%	N	%
No menses	2	0.2	1	0.1
≥ 8 days late	117	12.1	132	13.9
3-7 days late	144	14.9	134	14.1
2 days late to 3 days early	559	57.9	538	56.7
4-7 days early	141	14.6	142	15.0
Missing	5	0.3	2	0.2

Reviewer comment: The MO reviewed data from 853 women who had at least one of the following findings at their follow-up visit: 1) duration of next menses of <3 or >6 days; 2) bleeding less than or much more than "normal," or 3) bleeding NOT within +/- 4 days of the next expected menses. The reason for the requested listing is that any one of these findings might be associated with a treatment failure (pregnancy) and symptoms associated with a threatened or inevitable early miscarriage. There was little confirmatory urine or serum hCG data on this large subset of women, so the sponsor's assumption was that the onset of any menstrual bleeding was indicative of success (i.e., no pregnancy).

The results of the MO analysis from the data on these 853 women with an "abnormal" next menses showed the following:

1. **There were 433 women who took levonorgestrel and 420 who had the Yuzpe regimen; the MO analysis agrees with the sponsor's statement above that the percentages in each of the categories were almost identical in the two groups (levonorgestrel vs. Yuzpe).**
2. **235 women (12.0% of the 1955 women in the Efficacy Population) had >6 days bleeding, and 42 women (2.1% in the Efficacy Population) had <3 days bleeding.**
3. **240 women (12.3% of the 1955 women in the Efficacy Population) had bleeding less than normal, and 40 women (2.1% in the Efficacy Population) had bleeding much more* than normal.**
   ***Women could record on the daily diary card that their bleeding was more than or much more than normal. The MO requested data only for women with much more than normal. Hence, the sponsor's finding that 12-13% of the women in the study had bleeding more than their normal menses would include all women with both more and much more bleeding than normal.**
4. **426 women (21.8% of 1955) had their next menses >4 days later than expected, and 160 women (8.2%) had their menses >4 days earlier than expected.**
5. **The most important finding is that there did not appear to be any obvious differences between treatment arms regarding the data concerning menstrual bleeding patterns at follow-up.**

Serious Adverse Events

One death occurred during the study. Subject 004-Z from Jos, Nigeria died of meningitis two weeks after enrollment. There is no information to suggest that her death was associated with use of levonorgestrel. The subject was a 23 year old woman, gravida 2, para 1, aborta 1, who had never used emergency contraception; however, she had used oral and injectable contraception in the past. She was admitted to the study after unprotected intercourse. She did not have a pelvic examination or pregnancy test on enrollment, nor was a sample obtained for a retrospective pregnancy test. She was not receiving any concomitant medication. She received one dose of levonorgestrel after admission to the study. There is no additional information because she died before her scheduled return visit.

Reviewer's comment: The CRF was reviewed and it did not appear that this death was related to the study drug. Meningitis epidemics are common in Nigeria and the resultant death was most likely related only to the serious infection.

Pregnancy

Forty-two women were found to be pregnant after treatment. The sponsor's retrospective hCG analysis revealed that four of the 42 were already pregnant at enrollment. For five pregnant women, pregnancy status at admission was unknown. All pregnancies were intrauterine. Five of the 42 women continued their pregnancies with normal outcomes, while the others opted to terminate the pregnancy. Outcome of Pregnancy Forms are provided in the NDA. There were no reports of congenital anomalies in women receiving levonorgestrel in the pivotal study or in any of the clinical studies or literature cited in the NDA.

Reviewer's comment: The MO agrees with the sponsor's conclusion that an increased risk of congenital anomalies among women for whom the treatment failed or women who might mistakenly take the drug after they are already pregnant is very unlikely. The proposed labeling for this product

does not recommend routine pregnancy testing prior to initiation of treatment and is considered reasonable by the MO.

Ectopic Pregnancy Risk

Ectopic pregnancy is a potential risk of progestin-only contraception; however, the reports of ectopic pregnancies are sparse. They do not appear to occur more in women using emergency contraception than in the untreated population. The controlled and uncontrolled trials have been reviewed and summarized by the sponsor for possible ectopic pregnancies. If ectopic pregnancies occurred in up to 10% of pregnancies as predicted by the literature (McCann 1994), they would have expected to see three ectopic pregnancies in the five studies conducted by WHO/HRP. None were observed. Among the 30 pregnancies reported in 30 other small studies of levonorgestrel 0.75 mg, no ectopic pregnancies were reported. One ectopic pregnancy is noted in the literature. WCC is attempting to obtain a copy of this 1988 Hungarian study report (Hetényi). WCC concludes that there appears to be no increase in the rate of ectopic pregnancy after use of levonorgestrel for emergency contraception and no reason to suggest any such association in the proposed product labeling.

Reviewer's comment: Although no ectopic pregnancies were reported in the five WHO/HRP studies, the number of overall pregnancies reported is small (only 39 levonorgestrel failures with 23 unknown outcomes, 12 pregnancy terminations, and 4 normal births). A word of caution in the label would be prudent, since the studies performed were not powered to detect any increased risk of ectopic rates, and since progesterone only contraceptives include such a caution statement for this class of drugs.

Concomitant Therapy

Women on continuous treatment with a prescription drug were not necessarily excluded from participating. The type of medicine was the determining factor, but guidelines were not explicit in the protocol. Listings of all subjects receiving concomitant medication were provided.

One subject received levonorgestrel and carbamazepine (Mazetol) concomitantly and did not become pregnant. Other concomitant medications reported in the levonorgestrel arm of the clinical trial included broad spectrum antibiotics (including tetracycline, sulfonamides, doxycycline, penicillins, cephalosporins, anti-malarials), analgesics (including paracetamol, ibuprofen, aspirin), beta-agonists and inhaled steroids for asthma, prednisolone, thyroxin, iron, decongestants, guaifenisin, propranalol, insulin, and Chinese herbal remedies. Additional doses of hormonal contraceptives were also noted.

Theoretically, the effectiveness of levonorgestrel may be reduced in women receiving long-term therapy with hepatic enzyme-inducing drugs such as the anticonvulsants phenytoin, carbamazepine, and barbiturates, and the antituberculosis drug rifampin.

Other oral contraceptives have been shown to alter the kinetics of concomitantly administered drugs. The clearance of certain drugs undergoing oxidation, such as benzodiazepines (chlordiazepoxide, diazepam), and nitro-reduction (nitrazepam, theophylline, prednisolone, caffeine, and cyclosporin) is reduced in these subjects. The clearance of drugs undergoing glucuronidation (*e.g.*, temazepam, salicylic acid, paracetamol, morphine, and clofibric acid) may be increased in the presence of combination oral contraceptives. These effects have not been reported with levonorgestrel alone. It is unlikely short term administration (2 doses) of levonorgestrel would have any effect on the microsomal enzyme metabolism of the above mentioned drugs. (Back)

Reviewer comment: The MO agrees with the Sponsor's comments. Concomitant medications should not be a contraindication to taking PLAN B™ for emergency contraception unless future data demonstrates otherwise.

McCann wrote an extensive review ('94) of the clinical safety literature on behalf of the FDA to support new labeling of progestin-only contraceptive pills (POPs) and then updated the review ('98) for this NDA. A summary of sparse data concerning potential AEs associated with levonorgestrel and POPs follows from the 1994 and 1998 reports by McCann:

- Cardiovascular: blood pressure is not altered and risk of CV disease is not increased
- GI organs: does not appear to be associated with liver, gallbladder, or inflammatory bowel disease
- Ectopic pregnancy: up to 10% of pregnancies in POP users are ectopic, but their incidence of ectopics is no higher than among women not using any oral contraception
- Congenital anomalies: there has been no reported associations
- Lactation: no effect on breastfeeding performance, either in the quality or quantity of the milk or risk to the infant
- Menses: irregular bleeding is common
- PID: may be decreased
- HIV: the effect is unknown
- Metabolic: lipid metabolism is negligibly affected. Carbohydrate metabolism is sometimes slightly altered. No effect on bone density. No association with thyroid disease.
- Neurologic: reduce the likelihood of seizures
- Hematologic: no effect on coagulation factors
- Cancer: may provide a modest protective effect for endometrial and ovarian cancer

4.10 General Safety Conclusions

Safety data from more than 15,000 women in studies of various doses of levonorgestrel for emergency contraception, occasional postcoital contraception, or routine postcoital contraception showed that levonorgestrel, taken postcoitally, is well tolerated. Altogether, the NDA provides clinical data on women from 29 countries. The data in this NDA represents the bulk of literature and unpublished study reports found as a result of an extensive literature search. The literature search did not uncover any serious adverse events, and the side effects reported were consistent across the studies. Furthermore, no serious adverse events have been reported from three ongoing studies of levonorgestrel or from introductory trials of Postinor-2 in three countries. Menstrual disturbances, particularly intermenstrual bleeding or spotting, are the most common complaint in routine postcoital use, and are apparently not dose-related. Menstrual disturbances should not be a factor in use of levonorgestrel 0.75 mg for the proposed indication, that is, for one-time emergency contraception.

With respect to pregnancy outcomes, the literature review suggests no association between postcoital levonorgestrel use and an increased risk of ectopic pregnancy, although this is a concern with progestin-only oral contraceptive pills. 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. Because there is no reason to believe that pregnant women taking the treatment would risk harm to a developing fetus, the proposed labeling for the product does not recommend routine pregnancy testing prior to initiation of treatment. No pregnancy test will be packaged with the proposed product.

Levonorgestrel was well tolerated by women in this large multicenter, international study. Nausea, vomiting, dizziness, and fatigue were much less common in women who received levonorgestrel. The reduction in gastrointestinal symptoms may have facilitated compliance with treatment with levonorgestrel, as demonstrated by the reduction in the need for a third dose (4.8% of levonorgestrel users vs. 9.1% of Yuzpe users). Other adverse events were less common in the group assigned to levonorgestrel, but the differences were not significant. The time to resumption of menses as well as the pattern of bleeding was similar for women in the two treatment groups.

5.0 Labeling

The original proposed PLAN B™ labeling from the sponsor was not adequate. The labeling proposed by the Division was based on a composite of the following labels and documents:

1. Proposed PLAN B™ label
2. FDA labeling guidance for progestin-only oral contraceptive pills (POPs)
3. Micronor® tablets label (POPs category with 0.35 mg norethindrone)
4. Ovrette® tablets label (POPs category with 0.0375 mg levonorgestrel)
5. PREVEN™ Emergency Contraceptive Kit label (ECP category)
6. This medical officer review: concerning efficacy and safety

The sponsor was contacted and sent a copy of the FDA proposed label during the week of May 17-21, and further changes were made after discussions with the sponsor. The primary difficulty with the label was the fact that this is the first product to be approved by the FDA that is a progestin-only for emergency contraception. The only approved product for emergency contraception (approved in September 1998) is a combination of an estrogen (ethinyl estradiol) and the same progestin (levonorgestrel). Multiple labeling negotiations with the sponsor occurred during this NDA review. Labeling submitted by the sponsor on June 22, 1999 was considered acceptable as the final printed label.

6.0 Reviewer's Discussion and Overall Comments

It is clear that Plan B™ (progestin-only regimen of two doses of levonorgestrel 0.75 mg) is effective and safe for emergency contraception. The comparative Ho and Kwan study of ~900 women in Hong Kong presented data demonstrating similar efficacy for the two-dose Plan B compared to the recently approved two-dose Yuzpe regimen. WHO Study 92908 with 1998 women showed statistical evidence of superiority of Plan B over Yuzpe, the interpretation of which is limited by the trial design issues as discussed in this review. Both studies demonstrated statistically significant less nausea and vomiting with Plan B. Both studies were prospective, comparative, randomized, double-blind and used the same study drugs in slightly different regimens. The WHO/HRP pivotal study was multi-center, international, enrolled women within 72 hours after intercourse, and offered a third dose. The Ho and Kwan study was single-center (Hong Kong), enrolled only women within 48 hours after intercourse, and did not offer a third dose.

There were three primary objectives in the pivotal WHO Study 92908:

1. To confirm the Ho and Kwan finding that the 2-dose levonorgestrel treatment for EC had the same effectiveness as the Yuzpe regimen
2. To confirm the Ho and Kwan finding that the 2-dose levonorgestrel treatment had fewer side effects than the Yuzpe regimen
3. To assess whether the same effectiveness could be achieved if the start of treatment were extended to 72 hours

All three of these study objectives were met.

6.1 Study Design Deficiencies

The major flaw in the pivotal study was the lack of hCG pregnancy testing, either urine or serum, at the baseline (entry) visit and especially at the end-of-study visit. The surrogate endpoint was the occurrence of any vaginal bleeding, no matter when it occurred relative to the next expected menstrual period. Thus, the true incidence of pregnancies (failures) was not accurately determined. Likewise, the urine hCG testing of only 51% of the subjects at the entry visit is concerning. It is of note that the only center with serum hCG testing of all subjects at entry (Panama with 68 women) produced three of the four pregnant women ultimately eliminated from the sponsor's Efficacy Population.

Another weakness with the study design is the collection of data for AEs. The MO reviewed ~50 diary cards from 16 sites and the data recorded were simply a yes/no for the 10 listed adverse events. The AE data was requested and analyzed for the first seven days after therapy was initiated; no quantification (mild, moderate, severe) or specific time recording was attempted.

The MO evaluable population excluded five women; three were pregnant by hCG testing at the entry visit and two (06-96 and 789-36) had intercourse at a time in their cycle incompatible with a possible conception. The sponsor's evaluable Eligible Population included four women with a positive hCG test at admission; one of these subjects (1162-28) was determined by the MO as evaluable and not pregnant at the entry visit. Because of the differences in how many subjects were included in which populations, the sponsor's and MO's pregnancy rates, relative risks, and prevention fractions differ. These differences and their interpretation are discussed in this MOR.

6.2 Potential Concerns

There are four areas of caution that became apparent during the overall review of this NDA: efficacy in Chinese women, efficacy with timing of first dose, risk of ectopic pregnancy, and product stability.

1. Efficacy of Plan B in Chinese women: in the MO evaluable population of 1955 women in both treatment arms, 50 % of the Plan B and Yuzpe pregnancies (failures) were from the four Chinese centers that comprised only 25% (500 women) of the population. Also, in the supportive Ho and Kwan study with 834 Chinese women, the pregnancy rates of 2.9 and 3.5% were higher than the historically expected 2% pregnancy rate. These facts suggest that emergency contraception with either Plan B or Yuzpe has less efficacy in Chinese women. Explanations for this observation are not clear, but labeling should reflect this finding.

2. Efficacy differences between 24 hour time blocks: higher pregnancy rates were clearly noted among women who started either Plan B or Yuzpe 24 hours or more after intercourse. The highest pregnancy rates were in women who started treatment between 48 and 72 hours. The labeling of the PLAN B™ product should be written to encourage women to start the treatment as soon as is reasonably possible after intercourse. It is noted, however, that even among women who delay treatment, the levonorgestrel therapy retained efficacy; it prevented 61% of expected pregnancies among women who initiated treatment 48-72 hours after intercourse.

3. Risk of ectopic pregnancy in Plan B failures: ectopic pregnancy is a potential risk of progestin-only contraception. Although no ectopic pregnancies were reported in the five WHO/HRP studies on emergency contraception, the number of overall pregnancies reported is small (only 39 levonorgestrel failures with 23 unknown outcomes, 12 pregnancy terminations, and 4 normal births). A word of caution in the label would be prudent, since the studies performed were not powered to detect an increased risk of ectopic pregnancy.

4. Stability of the actual proposed product: see FDA chemist David Lin's report concerning the chemical stability of the Plan B product, levonorgestrel 0.75 mg, manufactured by

7.0 Final MO Recommendations:

1. Approval of Plan B is recommended. It is at least as effective as the Yuzpe regimen. It cannot be granted efficacy superiority to Yuzpe for several reasons:

- The supportive Ho and Kwan study clearly shows equivalency, and both treatment arms in the large Efficacy Population showed pregnancy rates (2.9% Plan B; 3.5% Yuzpe) higher than the expected rate of 2%. In an analysis excluding all women who had additional acts of intercourse, the pregnancy rates were 2.4% levonorgestrel and 2.7% Yuzpe.

- Only a single trial may have demonstrated statistical evidence of superiority, but that trial suffered from the design flaw of not testing accurately with urine or serum hCG for pregnancy at baseline or at the end of the study.
- The efficacy results (pregnancy rates, relative risk, and prevention fractions) differ depending in which population is chosen and how the populations are defined; for example, the difference in the pregnancy Prevented Fractions in the sponsor's Perfect Use Population were not statistically significant.

2. Plan B is superior to the Yuzpe regimen for the side effects (AEs) of nausea and vomiting.

3. Plan B is effective if treatment is started within 72 hours of unprotected intercourse, but the label should clearly reflect the fact that earlier treatment is associated with better efficacy.

/S/ 6/22/99
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Medical Officer, DRUDP

/S/ 6/23
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cc: HFD-580 division file/ Rarick/ Mann/ Mercier/ Davis/ Lin/ Hoberman/ Parekh
NDA 21,045 file

MO Table: Study 92908 Failures (Pregnant subjects)

Site and ID #	Age, Parity	Coitus OV ±	First dose	Other coitus	Sx's*	ADM Lab	Confirm IUP	REMARKS	Perfect Use
Sweden 01-60	27 P0	-1	35 hr	X 1, condom	N, HA, Diz, W/F	Urine	U, Sono @ 5 wk	YZ method failure	No
01-82	23 P0	-2	64.5	None	None	Urine	Urine	LNG method failure	Yes
Delhi 06-71	25 P0	-1	13.5	None	None	Urine Blood	U, Sono @ 5 wk	YZ method failure; delivery 12 mo. Later	Y
06-96	32 P2	-13 Day 6	35	X 4, condom	None	Blood not tested	Sono @ 5 wk	YZ; LMP2/26; sex 3/3; Sono conception 3/19. NON-evaluable	N
Pittsbrg 078-26	22 P2	+9	35 +14	X 1, N9	N,V, HA W/F,Br	Blood +	Sono	YZ; Pregnant before Rx; NON-evaluable	N
078-74	23 P0	0	44	None	All but Pain	Urine Blood	Sono @ 5 wk	YZ method failure	Y
Lagos 302-03	33 P5	0	10.5	X 1, condom	N, Pain	None	Urine	LNG method failure	N
Man-chester 789-19	21 P1	-3	26	X 12, condom	None	None	Urine	YZ User failure; Unreliable coital Hx. Took 3rd dose.	N
789-36	21 P0	-10	140	X 2, condom	N, Dizy, W/F	None	Urine	YZ User failure; NON-evaluable	N
789-59	26 P1	-2	44 +11	None	All but Br	None	Urine	YZ method failure	Y
ʻama 2-03	29 P1	0	45	X 3, condom	None	Bld-? Result	U, Sono @ 7 wk	LNG. LMP 7/7. Sono conception 7/3. Unreliable. IUP before Rx. NON- eval	N
1162-28	26 P1	0/+1 11/7 coitus	17	X 2, condom	HA, Dizy Pain	None	U, Sono concept 11/04	YZ failure + coitus X 2. Investigator thought concept 10/22. MO: evaluable	N
1162-44	20 P0	+4	38	Yes		Blood +	N.A.	YZ use. IUP before Rx. NON-eval	N
Beijing 1378-16	40 P0	-2	51.5	X 1, no BC	N, V	Blood	Sono @ 5 wks	YZ method failure	N
1378-25	32 G4P0	-2	22	None	None	Blood	Sono @ 6+ wk	LNG method failure. CRF said IUP b/4 Rx	Y
1378-31	24 P0	-2	21.5 12+2	X 4, no BC	N,V,HA, Br, Pain	None	U, Sono concept 11/4	YZ failure: Coitus 11/1. Took 3rd dose. Coitus X 4 after Rx.	N
1378-50	33 G4P1	-4/-3	36 hr	X 2, condom	N	Blood	Sono, Concept 11/13	YZ failure: Coitus 11/7. Coitus X 2 after Rx.	N
1378-93	36 G2P1	-3	14	None	None	Blood	Sono, Concept 11/22	YZ method failure Coitus 11/18.	Y
Beijing 1378-97	43 G1P1	-1	35 12+14	None	N,V,HA Diz, W/F	Blood	No U or Sono listed	YZ method failure Vomit 4 hr after 1st dose. 43 yo, regular cycle.	Y

*Sx's = symptoms. N=nausea, V=vomiting, HA=headache, D or Diz=dizzyness, W/F=weak, fatigue, Br=breast ptoms, Pain=abdominal pain or cramps.

Site and ID #	Age, Parity	Coitus OV ±	First dose	Other coitus	Sx's	ADM Lab	Confirm IUP	REMARKS	Perfect Use
Shanghi 1326-06	32 G1P1	-1	13	X 1, condom	None	Urin -	Urin+ Sono +	YZ method failure. Coitus = conception date.**	N
1326-21	29 P0	-2	37	None	None	Urin -	Sono +	YZ method failure. Coitus = conception date.**	Y
1326-47	24 G1P1	-3	43	X 1, condom	None	Urin -	Sono +	YZ method failure. Coitus = conception date.	N
1326-99	28 G2P1	-2	13	None	N, V	None	Sono +	YZ method failure. Coitus = conception date.	Y
Nanjing 1423-37	32 G3P1	-1	58	None	Diz, W/F Diarrhea	Urin -	Sono +	YZ fail. Coitus = conception: bisthmus for abdo Sx	Y
1423-52	28 G1P1	-2	43	X 3, condom	N, W/F	Urin -	Sono +	YZ method failure. Coitus = conception date.	N
1423-128	26 G1P0	+1/2	58	None	N, HA	Urin -	Sono +	YZ method failure. Coitus = conception date.	Y
1423-142	25 G1P0	-1	60	None	None	Urin -	Sono +	LNG method failure. Coitus = conception date.	Y
1423-147	30 G1P1	-1	59	None	N, Diz, Pain, W/F	Urin -	Sono +	LNG method failure. Coitus = conception date.	Y
1423-185	26 G3P1	-4	56	None	N, Diz, W/F	Urin -	Sono +	YZ method failure. Coitus = conception date.	Y
Tianjin 1539-30	24 G2P0	-1	61.5	X 5, condom	N, V	Urin-	Sono +	YZ fail. **Sono. Dr. Weiyu thought pt. pregnant before	N
1539-35	31 G2P1	-1	42	None	N only	Urin-	Sono+	LNG failure. Coitus = conception date.	Y
39-51	35 G2P1	-4	60	X 2, condom	N	Urin-	**Sono	LNG failure: user vs. method.	N
Sagamu 1757-533	36 G7P7	-2	9	X 1, no bc	N, W/F	Urin-	Urin+ No sono	YZ fail.	N
North-bridge 1983-45	22 G0P0	+2	34 +11	X 1, no bc	None	Urin-	Urin+	LNG user failure. Card unreliable for coitus Hx.	N
Christ-church 2009-17	31 G2P2	+4	61	X I, condom	N, Pain	None	Urin+ No sono	LNG fail. No adm labs. Ov +4. UTI rx'd at adm	N
2009-27	24 G1P1	+3	61	None	N, Diz, Pain	Urin-	Urin+ No sono	YZ method failure. Ov +3.	Y
Auck-land,NZ 2008-04	36 G4P3	+0	44 12+4	X 4, condom	All, but no V	None	Urin+ Sono+	LNG fail. Coitus = conception date. 3rd dose taken.	N
2008-08	36 G2P2	-2	23	X 4, Condom	N, HA, Pain	Urin-	Urin+ Sono+	YZ fail. Coitus 2/29. Sono conception 3/6.	N
2008-31	25 G0P0	+4	42.5	X 2, condom	N, V, HA, Diz	None	Urin+ Sono+	YZ fail. Coitus = conception date.	N
Well,NZ 2010-21	21 G0	-2	24	X 3, Condom	Br, Pain	Urin-	Urin+ No sono	YZ fail. MO: user failure.	N
2010-41	19 PO	+0	41	None	N,HA,Br Diz,Pain	Urin-	Urin+ No sono	YZ method failure.	Y
2010-97	22 P1	+0	39+2, +12	X 1, Condom	N,V, Pain	Urin-	Urin+ No sono	YZ method fail. 3rd dose taken.	N
Site and ID #	Age, Parity	Coitus OV ±	First dose	Other coitus	Sx's	ADM Lab	Confirm IUP	REMARKS	Perfect Use

** Sonogram conception date agrees with date of unprotected coitus

NDA 21-045

PLAN P™
(levonorgestrel) Tablets

JUL 12 1999

Safety Update Review for NDA 21-045: all safety update submissions for this NDA were reviewed by the medical officer. There were no additional serious AEs, or other AEs that were of concern. The conclusion is that the product is safe and should be used as labeled.

/S/

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DRUDP

/S/ 7/12/99
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