CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-045/S011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	**21-045**
Brand Name:	**Plan B®**
Generic Name:	**Levonorgestrel**
Sponsor:	**Women's Capital Corporation**
Relevant IND(s):	**45,796**
Date of Submission:	**April 22, 2003 (SE6-011)** **February 24, 2004 (SE6-011, Serial No. 125)**
Type of Submission:	**sNDA**
Code:	**Request for Switch to OTC**
Formulation:	**Tablet**
Strength:	**0.75 mg**
Indication:	**Emergency Contraception**
Reviewer:	**Myong-Jin Kim, PharmD**
Team Leader:	**Ameeta Parekh, PhD**
OCPB Division:	**DPE-II**
OND Division:	**Reproductive & Urologic Drug Products**

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I. Executive Summary

Plan B® (levonorgestrel, LNG, 0.75 mg tablet, NDA 21-045) was approved by the FDA on July 28, 1999 as a prescription product for emergency contraception in all women of reproductive age. This product is used as a 2-tablet regimen with the first tablet to be taken as soon as possible within 72 hours after unprotected sexual intercourse or a known or suspected contraceptive failure and the second tablet to be taken 12 hours later. A third dose is recommended if vomiting occurs within 4 hours after either required dose.

Women's Capital Corporation (WCC) submitted the Supplement to this approved NDA to request a prescription to over-the-counter (Rx-to-OTC) switch on April 22, 2003. The dosage and instructions for use remain the same. The sponsor proposed that the Rx-to-OTC switch is needed because the current prescription requirement presents a barrier to timely access and because delays in treatment reduce efficacy significantly.

The sponsor submitted a pharmacokinetic study (PK-002) conducted in 22 healthy females aged 12 to 16 years following a single oral administration of 0.75 mg LNG Plan B tablet. In addition, the sponsor resubmitted the PK data from Study PK-001 (original submission to NDA 21-045) conducted in 16 healthy females aged 18 to 45 years following a single oral administration of 0.75 mg LNG Plan B tablet. The sponsor also submitted copies of the published literature on the PK studies of alternative LNG dosing regimens (one single 1.5 mg dose of LNG or two separate administrations of 0.75 mg LNG at either 12- or 24-hour time intervals).

Review of PK Studies 001 and 002 revealed differences in pharmacokinetics of LNG between adolescent and adult female subjects. The sponsor was requested to address the possible contributing factors and the clinical significance of these apparent differences in the two groups. The response to this Information Request Letter (February 5, 2004) was received dated February 24, 2004 (SE6-011, Serial No. 125). The possible factors likely to contribute to these differences as well as the sponsor's response were evaluated. There is no inherent reason to believe that adolescent females would have different pharmacokinetic characteristic compared to adult females. These apparent differences are possibly related to limitations associated with cross study comparisons and study design differences between the two studies.

A. Recommendations

From the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics, Human Pharmacokinetics and Biopharmaceutics section of the sNDA 21-045 (SE6-011) is *acceptable.*

Phase IV commitment

None.

B. Summary of Clinical Pharmacology and Biopharmaceutics Findings

In a cross-study comparison, the mean values of C_{max} and AUC_{inf} of LNG following a single oral administration of Plan B tablet were about 47 % (a mean ratio of adolescents/adults of 0.53, 90% CI of 0.41, 0.68) and 23 % (a mean ratio of adolescents/adults of 0.77, 90% CI of 0.61, 0.96) lower in healthy adolescent females compared to healthy adult females, respectively. In adolescent female subjects, the geometric mean C_{max} of LNG was 6.72 ng/mL (CV 45.8%) and the mean AUC_{inf} was 86.14 ng*hr/mL (CV 42.9%). In adult females, the geometric mean LNG C_{max} was 12.8 ng/mL (CV 43.7%) and the mean AUC_{inf} was 112.5 ng*hr/mL (CV 40.0%).

The sponsor indicated (Response Letter dated February 24, 2004) that these apparent differences are not likely to be clinically significant. The conclusion was based on the literature references showing a similar efficacy from different formulations of LNG 0.75 mg tablets with significantly different bioavailability (He C *et al* 1990, Contraception 41:557-67) as well as demonstrated efficacy of LNG 0.4 mg tablet in postcoital contraception (Kesseru E *et al* 1973, Contraception 7:367-79). In addition, the sponsor addressed the following possible factors that might have contributed to the observed differences: differences in the fed status and physical activity, difference in time of drug administration, possible diurnal variation in pharmacokinetics and metabolism, and ethnic differences in LNG pharmacokinetics. These possible factors were also evaluated by this reviewer and are discussed further.

The published literature data indicate that pharmacokinetics of LNG following a single oral dose of LNG 0.75 mg tablet in adult females show high variability. The mean values of C_{max} and AUC_{inf} LNG ranged from 5-14 ng/mL and 116-164 ng*hr/mL, respectively (note: some of the PK values are expressed in nmol/L and nmol*hr/L units in the table below). Given that LNG pharmacokinetics are highly variable, the observed differences in systemic exposure from the cross-study comparison in the adult and adolescent female subjects should be interpreted with a caution. It is not clear whether the lower systemic exposure observed in adolescent females is clinically meaningful.

Literature Data: Pharmacokinetic Parameters of LNG Following a Single Oral Dose of LNG in Adult Females (arithmetic mean ±SD, range)

Reference	Kook et al (PK-001)	Tremblay et al	Johansson et al	Johansson et al	Landgren et al	He et al	Shi et al
Formulation Strength	Plan B 0.75 mg	Norlevo 0.75 mg	Norlevo 0.75 mg	Norlevo 1.5 mg	Gedeon Richter 0.75 mg	Postinor 0.75 mg	Gedeon Richter 0.75 mg
Race (study site) (subject #)	Caucasian/Black /Asian (U.S.) (n=9)	Caucasian (South Africa) (n=8)	NR (Dominican Republic) (n=5)	NR (Dominican Republic) (n=5)	Swedish (Sweden) (n=10)	Chinese (China) (n=10)	Chinese (China) (n=6)
C_{max} (ng/mL)	14.1±7.7 (6.7-39)	30.7±11.4 nmol/L	26.7±10.2 nmol/L (17.7-42.9)	39.6±4.9 nmol/L (32.9-46.4)	16nmol/L	11.2±3.4 (8.1-18.4)	8.6±2.0 (5.3-10.1)
T_{max} (hr)	1.6±0.7 (1-4)	2.3±0.7	1.8±0.4 (1.3-2.2)	2.6±0.7 (1.6-3.4)	2	1.9±0.6 (1-2.7)	3.3±1.0 (2-4)
AUC_{inf} (ng*hr/mL)	123.1±50.1 (62.5-222.1)	527±304 nmol*hr/L	NR	948±229 nmol*hr/L (703-1212)	NR	124±42.8 (66.8-177)	116.2±41 (67-160)
Assay	GC/MS/MS	RIA	RIA	RIA	RIA	RIA	RIA

RIA: Radioimmunoassay, NR: Not reported, 1 nmol/L = 0.312 ng/mL, Landgren *et al* 1989 Contraception 39:275-89, He C *et al* 1990 Contraception 41:557-67, Johansson *et al* 2002 Human Reproduction 6:1472-6, Kook *et al* 2002 Contraception 66:73-6, Shi *et al* 1988 Contraception 37:359-69, Tremblay *et al* 2001 Contraception 64:327-31.

The study designs of PK-001 and PK-002 were compared to explain the differences in the LNG exposure. The study designs differed in the following aspects: In Study PK-002, fasting occurred for 4 hours before dosing instead of 8 hours, and lasted for 3 hours post-dose instead of 4 hours. However, it should be noted that actual fasting was not monitored since the adolescent subjects were instructed to report to the study site after fasting for at least 4 hours. Dosing occurred between 4 pm and 7 pm instead of at 8 am. In addition, although the duration of blood sampling was the same for both studies, fewer blood samples were taken (14 versus 19 samples). The same analytical laboratory using the same assay method was used to determine LNG concentrations in Studies PK-001 and PK-002.

Study Design Comparison		
Study	**PK-001**	**PK-002**
Subjects	Healthy adult females (n=16)	Healthy adolescent females (n=22)
Study Design	A prospective, single-period, single-center, open-label, single dose study	A prospective, single-period, single-center, open-label, single dose PK study
Age (yrs)	28 ± 9 (19 – 44)	15 ± 1 (13 – 16)
Weight (kg)	65.3 ± 9.9 (51 – 79.5)	59.5 ± 9.4 (41.8 – 77.3)
BMI	23.7 ± 2.4 (19.3 – 26.5)	23.8 ± 3.1 (18.5 – 28.9)
Race, n (%)	9 White (56%), 6 Black (38%), 1 Asian/Pacific Islander (6%)	12 Black (54%), 5 Multiracial (23%), 4 Latina (18%), 1 Asian (5%)
Fasting	Overnight 8 hr fasting pre-dose, 4 hr fasting post-dose	4 hr fasting pre-dose, 3 hr fasting post-dose
Dosing time	8 AM	Between 4 PM and 7 PM
Blood draw	72 hrs post-dose, 19 blood samples (pre-dose, 0.5, 1, 1.25, 1.5, 1.75, 2, 4, 6, 8, 10, 12, 15, 18, 24, 30, 36, 48, 72 hr)	72 hrs post-dose, 14 blood samples (pre-dose, 0.5, 1, 1.25, 1.5, 1.75, 2, 4, 8, 10, 12, 24, 48, 72 hr)

To explain the lower systemic exposure of LNG observed in adolescent females, the possible effects of food intake, ethnicity/race, body mass index, time of drug administration, intra- and inter-subject variability of LNG, differences in SHBG levels, study design factors, and limitations of cross-study comparison on LNG pharmacokinetics were evaluated using literature references and the two PK studies (PK-001, PK-002). It is unclear why the young adolescent females showed the lower C_{max} and AUC compared to the adult females.
The knowledge of the PK of LNG when used for emergency contraception and the selection of the dose currently recommended is based on previously existing data. The recommendations for use of LNG are based on extensive clinical experience and not on pharmacokinetic data (Tremblay *et al* 2001, Contraception 64:327-31). In addition, the current LNG regimen of 12 hour interval was selected based on prior experience.

There are limited literature data to evaluate the PK/PD relationship of LNG as an emergency contraceptive. In a comparative study of Postinor® (Gedeon Richter Ltd., Hungary, similar to Plan B formulation) and the Chinese manufactured pill (Beijing No. 3 Pharmaceutical Factory) with 0.75 mg of LNG, the similar clinical effectiveness (a method failure of 1.1 % per treated cycle) with both formulations was observed when used for postcoital contraception. However, lower LNG serum concentrations were attained with the Chinese formulation (mean values: C_{max} of 5.9 ng/mL, AUC_{inf} of 92.3 ng*hr/mL) than after the administration of Postinor (mean values: C_{max} of 11.2 ng/mL, AUC_{inf} of 124 ng*hr/mL) (He *et al* 1990, Contraception 41:557-67, He *et al* 1991, Int J Gynecol Obstet 36:43-8).

Variability of LNG
Literature data indicate that there are marked intra-subject variability (23 – 80%) and inter-subject variability (2- to 4-fold) in LNG pharmacokinetics following 0.75 mg LNG tablets (He *et al* 1990, Contraception 41:557-67, Shi *et al* 1988, Contraception 37:359-69, Fotherby K 1995, Clin Pharmacokinetics 28:203-15). It is generally unknown what the sources of variability are. Age has not been formally studied as a contributing cause of variability (Fotherby K 1995, Clin Pharmacokinetics 28:203-15).

Race
No formal studies have evaluated the effect of race. However, clinical trials demonstrated a higher pregnancy rate in the Chinese population with both Plan B and the Yuzpe regimen (another form of

emergency contraception consisting of two doses of ethinyl estradiol 0.1 mg + LNG 0.5 mg). The reason for this apparent increase in the pregnancy rate of emergency contraceptives in Chinese women is unknown (Plan B Package Insert). The literature data have no racial and ethnic differences observed in other studies.

Body Mass Index (BMI)
In Study PK-002, the mean BMI of 22 healthy adolescent female subjects was 23.8 ± 3.1 (range, 18.5 – 28.9). The mean BMI of 16 healthy female subjects (PK-001) was 23.7 ± 2.4 (range, 19.3 – 26.5). Johansson *et al* reported that there was no correlation between BMI and LNG concentrations (C_{max}) achieved with any of the three regimens (one single 1.5 mg dose of LNG or two separate administrations of 0.75 mg LNG at either 12- or 24-hour time intervals) (Johansson *et al* 2002, Human Reproduction 17:1472-6).

SHBG levels
Johansson *et al* found a good correlation between baseline SHBG levels and LNG concentrations (C_{max}) when two doses of 0.75 mg LNG tablet were administered at either 12- (r = 0.79) or 24-hour time intervals (r = 0.86) (Johansson *et al* 2002, Human Reproduction 17:1472-6). However, SHBG levels were not measured in PK-001 and PK-002 to make a comparison.

Absorption
No specific investigation of the absolute bioavailability of Plan B in humans has been conducted. However, literature indicates that LNG is rapidly and completely absorbed after oral administration (bioavailability about 100 %) and is not subject to first pass metabolism. In adult females, LNG reached a C_{max} of 14.1 ± 7.7 ng/mL at an average of 1.6 ± 0.7 hrs following a single dose of Plan B tablet given in the morning (PK-001). In adolescent females, LNG reached a C_{max} of 7.5 ± 3.8 ng/mL at an average of 1.5 ± 0.7 hrs following a single dose of Plan B tablet administered in the early evening (PK-002).

Food Effect
The food-effect on the rate and the extent of LNG absorption after Plan B administration has not been evaluated. Literature search on the effect of food on LNG alone or LNG in combination oral contraceptives has not identified any studies to evaluate the potential food effect.

Distribution
LNG is primarily protein bound. Approximately 50 % is bound to albumin and 47.5 % is bound to sex hormone-binding globulin (SHBG) with only 2.5 % unbound (Plan B Package Insert; Fotherby K. 1995, Clin Pharmacokinetics 28:203-15).

Metabolism and Elimination
Following a single oral dosage, LNG does not appear to be extensively metabolized by the liver. In adult females, a mean terminal elimination half-life after one tablet of Plan B was 24.4 ± 5.3 hrs (PK-001). In adolescent females, a mean terminal elimination half-life after one tablet of Plan B was 22.2 ± 6.8 hrs (PK-002).

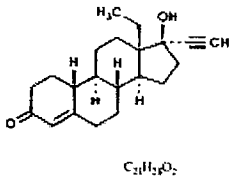
II. Question-Based Review

A. General Attributes

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Physico-chemical properties

- Structure of LNG



$C_{21}H_{28}O_2$

- Established Name: Levonorgestrel (LNG), USP
- Molecular Weight: 312.45
- Molecular Formula: $C_{21}H_{28}O_2$
- Chemical Name: d(-)-13 beta-ethyl-17-alpha-ethinyl-17-beta-hydroxygon-4-en-3-one

Formulation
The drug substance and drug product proposed for use in the OTC version of Plan B is manufactured by Gedeon Richter, Ltd. of Budapest, Hungary, the manufacturer of the prescription-only product. The formulation and dosage remain the same.

Each Plan B 100 mg tablet contains 0.75 mg of a single active steroid ingredient, LNG. The inactive ingredients present are colloidal silicon dioxide, potato starch, gelatin, magnesium stearate, talc, corn starch, and lactose monohydrate.

What is the proposed mechanism of action?
Plan B is believed to act as an emergency contraceptive principally by preventing ovulation or fertilization (by altering tubal transport of sperm and/or ova). In addition, it may inhibit implantation (by altering the endometrium). It is not effective once the process of implantation has begun.

What is the proposed indication and dose?
Plan B (LNG 0.75 mg tablet) is an emergency contraceptive that can be used to prevent pregnancy following unprotected intercourse. This product is used as a 2-tablet regimen with the first tablet to be taken as soon as possible within 72 hours after unprotected sexual intercourse or a known or suspected contraceptive failure and the second tablet to be taken 12 hours later.

B. General Clinical Pharmacology

What are the basic pharmacokinetic characteristics of levonorgestrel?

Pharmacokinetics (ADME)

Absorption
No specific investigation of the absolute bioavailability of Plan B in humans has been conducted. However, literature indicates that LNG is rapidly and completely absorbed after oral administration (bioavailability about 100 %) and is not subject to first pass metabolism. In adult females, LNG reached a C_{max} of 14.1 ± 7.7 ng/mL at a mean of 1.6 ± 0.7 hrs following a single dose of Plan B tablet given in the morning (PK-001). In adolescent females, LNG reached a C_{max} of 7.5 ± 3.8 ng/mL at a mean of 1.5 ± 0.7 hrs following a single dose of Plan B tablet administered in the early evening (PK-002).

The food-effect has not been studied.

Table 1. Pharmacokinetic parameters of LNG following a single dose administration of Plan B (LNG 0.75 mg) to healthy adult and adolescent female subjects (arithmetic mean ± SD).

Cross-study comparison	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC_{inf} (ng*hr/mL)
(PK-001, n=16) Healthy adult female subjects	14.1 ± 7.7	1.6 ± 0.7	24.4 ± 5.3	123.1 ± 50.1
(PK-002, n=22) Healthy adolescent female subjects	7.5 ± 3.8	1.5 ± 0.7	22.2 ± 6.8	94.5 ± 45.4

The published literature data indicate that pharmacokinetics of LNG following a single oral dose of LNG 0.75 mg tablet in adult females show high variability. The mean values of C_{max} and AUC_{inf} LNG ranged from 5-14 ng/mL and 116-164 ng*hr/mL, respectively.

Table 2. Mean (±SD, range) pharmacokinetic parameters of LNG following a single oral dose of LNG (Literature Data)

Literature Data: Pharmacokinetic Parameters of LNG Following a Single Oral Dose of LNG in Adult Females (arithmetic mean ±SD, range)							
Reference	Kook et al (PK-001)	Tremblay et al	Johansson et al	Johansson et al	Landgren et al	He et al	Shi et al
Formulation Strength	Plan B 0.75 mg	Norlevo 0.75 mg	Norlevo 0.75 mg	Norlevo 1.5 mg	Gedeon Richter 0.75 mg	Postinor 0.75 mg	Gedeon Richter 0.75 mg
Race (study site) (subject #)	Caucasian/Black /Asian (U.S.) (n=9)	Caucasian (South Africa) (n=8)	NR (Dominican Republic) (n=5)	NR (Dominican Republic) (n=5)	Swedish (Sweden) (n=10)	Chinese (China) (n=10)	Chinese (China) (n=6)
C_{max} (ng/mL)	14.1±7.7 (6.7-39)	30.7±11.4 nmol/L	26.7±10.2 nmol/L (17.7-42.9)	39.6±4.9 nmol/L (32.9-46.4)	16nmol/L	11.2±3.4 (8.1-18.4)	8.6±2.0 (5.3-10.1)
T_{max} (hr)	1.6±0.7 (1-4)	2.3±0.7	1.8±0.4 (1.3-2.2)	2.6±0.7 (1.6-3.4)	2	1.9±0.6 (1-2.7)	3.3±1.0 (2-4)
AUC_{inf} (ng*hr/mL)	123.1±50.1 (62.5-222.1)	527±304 nmol*hr/L	NR	948±229 nmol*hr/L (703-1212)	NR	124±42.8 (66.8-177)	116.2±41 (67-160)
Assay	GC/MS/MS	RIA	RIA	RIA	RIA	RIA	RIA

NR: Not reported, 1 nmol/L = 0.312 ng/mL,
Landgren *et al* 1989 Contraception 39:275-89, He C *et al* 1990 Contraception 41:557-67, Johansson *et al* 2002 Human Reproduction 6:1472-6, Kook *et al* 2002 Contraception 66:73-6, Shi *et al* 1988 Contraception 37:359-69, Tremblay *et al* 2001 Contraception 64:327-31.

Distribution

LNG is primarily protein bound. Approximately 50 % is bound to albumin and 47.5 % is bound to SHBG with only 2.5 % unbound (Plan B Package Insert; Fotherby K 1995, Clin Pharmacokinetics 28:203-15). Administration of LNG decreases SHBG levels with the maximum effect approaching after about 1 week. The study published by He *et al* reported a reduction in SHBG by about 8% after a single 0.75 mg dose of LNG at 24 hour post-dose (He *et al* 1990, Contraception 41:557-67). However, Johansson *et al* reported that SHBG levels remained essentially unchanged during the first 24 hours after LNG intake and noted the first decrease in the 48 hour sample (~10%), followed by a continuous, regular decrease down to ~60% of baseline values at Day 5 post-initiation of treatment (Johansson *et al* 2002, Human Reproduction 17:1472-6).

Metabolism and Excretion

Following a single oral dosage, LNG does not appear to be extensively metabolized by the liver. LNG is a low extraction drug and enterohepatic recirculation has not been reported. The primary

metabolites are 3alpha, 5beta- and 3alpha, 5alpha-tetrahydrolevonorgestrel with 16beta-hydroxynorgestrel also identified. Together, these account for less than 10% of parent plasma concentrations. Urinary metabolites hydroxylated at the 2alpha and 16beta positions have also been identified. Small amounts of the metabolites are present in plasma as sulfate and glucuronide conjugates.

In adult females, a mean terminal elimination half-life after one tablet of Plan B was 24.4 ± 5.3 hrs. In adolescent females, a mean terminal elimination half-life after one tablet of Plan B was 22.2 ± 6.8 hrs. Excretion following single dose administration as emergency contraception is unknown, but based on chronic, low-dose contraceptive use, LNG and its metabolites are primarily excreted in the urine, with smaller amounts recovered in the feces.

Variability in Pharmacokinetics

The literature data show 2- to 4-fold inter-individual variability in studies of LNG 0.75 mg (He *et al* 1990, Contraception 41:557-67, Shi *et al* 1988, Contraception 37:359-69). In the study by Shi *et al*, intra-individual variations in serum LNG concentrations ranged from 23 % to 80% (Shi *et al* 1988, Contraception 37:359-69).

- While steroids such as ethinyl estradiol can alter LNG pharmacokinetics via changes in SHBG, the significance of these effects on the bioavailability of LNG in an acute course of emergency contraceptive therapy is probably minimal (Kook *et al* 2002, Contraception 66:73-6).
- After a single administration of 0.75 mg LNG, plasma SHBG is decreased by 8.1 % (He *et al* 1990, Contraception 41:557-67). Since LNG binds with a high affinity to SHBG, the plasma concentrations of SHBG have been noted to influence LNG pharmacokinetics (Fotherby K. 1995, Clin Pharmacokinetics 28:203-15). However, Johansson *et al* reported that SHBG did not seem to influence LNG serum concentrations during the initial 2 days after treatment since SHBG was unchanged during the first 48 hours after initiation of treatment (Johansson *et al* 2002).
- Inter-individual differences in metabolism of LNG could contribute to the variability (Kook *et al* 2002, Contraception 66:73-6).

What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

He *et al* conducted a randomized, single dose, cross-over, relative bioavailability study of two marketed formulations of 0.75 mg LNG (Hungarian and Chinese formulations) in 10 healthy Chinese adult females. Blood samples were obtained up to 24 hours post-dose and the serum samples were analyzed for LNG by radioimmunoassay. The mean age and BMI of 10 subjects were 27.4 ± 3.7 years and 21.1 ± 2.8, respectively. Compare to a Postinor® tablet (Gedeon Richter Ltd., Hungary, similar to Plan B formulation), a Chinese pill showed lower relative bioavailability (about 28% for AUC_{0-24} and AUC_{inf} and 47 % for C_{max}).

Single Dose LNG 0.75 mg Tablet	Hungarian Formulation LNG 0.75 mg tablet (Postinor®) Mean ± SD (range)	Chinese Formulation LNG 0.75 mg tablet Mean ± SD (range)
*C_{max} (ng/mL)	11.2 ± 3.4 (8.1 – 18.4)	5.9 ± 1.7 (3.4 – 8.2)
*T_{max} (hr)	1.9 ± 0.6 (1 – 2.7)	3.1 ± 1.2 (2.1 – 5.3)
*AUC_{0-24} (ng*hr/mL)	92.2 ± 34.3 (54.0 – 152)	64.4 ± 21.9 (33.1 – 99.1)
AUC_{inf} (ng*hr/mL)	124.0 ± 42.8 (66.8 – 176.6)	92.3 ± 28.8 (42.7 – 121.8)

* denotes statistically significant difference between the Postinor and Chinese pill.
Note: Both the Chinese pill and Postinor contained 0.75 mg LNG and were from the same batch as those used in the clinical efficacy study.

Both formulations were studied in a clinical trial and shown to have a similar method failure rate of 1.1 % per treated cycle. In a randomized, double-blind, multi-center clinical study, contraceptive efficacy of Postinor and Chinese pill was evaluated during the peri-ovulatory period of one cycle in 361 healthy Chinese females aged 21 to 40 years. Subjects were administered a single dose of LNG 0.75 mg within 8 hours of first act of coitus and a second dose was taken 24 hours later. Subsequently, one LNG tablet was taken following each further act of coitus with a maximum of one tablet per 24 hour period. During the treatment cycle, subjects in Postinor Group (n=176) and Chinese pill Group (n=185) received a mean of 4.43 ± 1.04 (range, 2 – 7 tablets) and 4.13 ± 0.89 (range, 2 – 7 tablets) LNG tablets, respectively (He *et al* 1991, Int J Gynecol Obstet 36:43-8). The investigators concluded that despite the fact that in the clinical trial no significant differences were observed between the two LNG formulations in terms of contraceptive efficacy, there was a marked difference between them in their pharmacokinetics (He *et al* 1990, Contraception 41:557-67).

LNG doses as high as 1 mg to be used within 8 hours after intercourse have been reported. Lower LNG doses have been used within 1-8 hours of unprotected intercourse and they were associated with disruption of menstrual cycles. It was reported that a 30% pregnancy rate was reduced to 1% when the dose of LNG was increased from 0.15 mg to 0.75 – 1 mg (Landgren *et al* 1989, Contraception 39:275-89). The choice of 0.75 mg LNG dose was based on the established safety and efficacy of its use in many countries.

How does the systemic exposure change with various intrinsic and extrinsic factors?

C. Intrinsic Factors

Effect of Age
Pharmacokinetic data are not available for geriatric and pediatric (premenarchal) populations.

While Plan B is indicated as an emergency contraceptive in all women of reproductive age, labeling is not specific with respect to safety and efficacy of use in young female adolescents aged 16 years and younger. As part of the evaluation of efficacy of Plan B in the adolescents, the sponsor submitted a PK study (PK-002) conducted in 22 females aged 12 to 16 years after the oral administration of a single 0.75 mg dose. In addition, the sponsor resubmitted the comparison PK data from Study PK-001 conducted in 16 healthy females aged 18 to 45 years after the oral administration of a single 0.75 mg LNG tablet (NDA 21-045, previously reviewed by Dr. Ameeta Parekh in 1999).

The study designs of PK-001 and PK-002 are similar except for the following: In Study PK-002, fasting occurred for 4 hours before dosing instead of 8 hours, and lasted for 3 hours post-dose instead of 4 hours. Dosing occurred between 4 pm and 7 pm instead of at 8 am. In addition, fewer

blood samples were taken, 14 versus 19 samples.

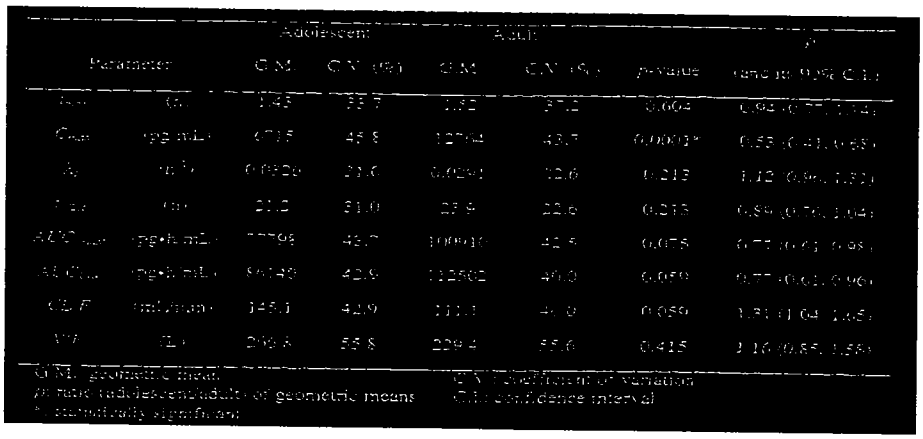
Study Design Comparison		
Study	**PK-001**	**PK-002**
Subjects	Healthy adult females (n=16)	Healthy adolescent females (n=22)
Study Design	A prospective, single-period, single-center, open-label, single dose study	A prospective, single-period, single-center, open-label, single dose PK study
Age (yrs)	28 ± 9 (19 – 44)	15 ± 1 (13 – 16)
Weight (kg)	65.3 ± 9.9 (51 – 79.5)	59.5 ± 9.4 (41.8 – 77.3)
BMI	23.7 ± 2.4 (19.3 – 26.5)	23.8 ± 3.1 (18.5 – 28.9)
Race	9 White (56%), 6 Black (38%), 1 Asian/Pacific Islander (6%)	12 Black (54%), 5 Multiracial (23%), 4 Latina (18%), 1 Asian (5%)
Fasting	Overnight 8 hr fasting pre-dose, 4 hr fasting post-dose	4 hr fasting pre-dose, 3 hr fasting post-dose
Dosing time	8 AM	Between 4 PM and 7 PM
Blood draw	72 hrs post-dose, 19 blood samples (pre-dose, 0.5, 1, 1.25, 1.5, 1.75, 2, 4, 6, 8, 10, 12, 15, 18, 24, 30, 36, 48, 72 hr)	72 hrs post-dose, 14 blood samples (pre-dose, 0.5, 1, 1.25, 1.5, 1.75, 2, 4, 8, 10, 12, 24, 48, 72 hr)

Adolescent (age 12 – 16 yrs) PK Study (PK-002)

A prospective, single-period, single-center, open-label PK study was conducted to determine the PK of LNG following oral administration of a single 0.75 mg Plan B tablet to healthy adolescent females aged 12 to 16 years. A secondary objective was to compare the PK values of LNG in healthy adolescent females to those previously determined in healthy adult females following the administration of a single 0.75 mg Plan B tablet (PK-001).

Healthy adolescent female subjects were administered orally a single Plan B 0.75 mg LNG tablet approximately 4 pm - 7 pm after fasting for at least 4 hours. Blood samples were obtained at pre-dose, and at 0.5, 1, 1.25, 1.5, 1.75, 2, 4, 8, 10, 12, 24, 48, and 72 hours post-dose. Subjects continued to fast for at least 3 hours post-dose.

Table 3. Statistical summary of LNG pharmacokinetic parameters in adolescent females (Study PK-002) and adult females (Study PK-001).



- In adolescent female subjects, the geometric mean LNG C_{max} was 6,715 pg/mL (CV 45.8%) and the mean AUC_{inf} was 86,140 pg/mL (CV 42.9%).
- There was a statistically significant difference between the adolescent and adult females

with respect to C_{max} (a mean ratio of adolescents/adults = 0.53, 90% CI of 0.41, 0.68).

- The difference between the two groups with respect to AUC_{inf} was borderline significant with a mean ratio (adolescents/adults) of 0.77 (90% CI of 0.61, 0.96).

COMMENTS:

- In cross-study comparison, the systemic exposure to LNG was somewhat lower (about 23 % lower AUC, 47 % lower C_{max}) in adolescent females than in adult females following a single 0.75 mg Plan B tablet. However, given that LNG pharmacokinetics are highly variable, it is unlikely that this apparent lower systemic exposure in the adolescent females would relate to diminished efficacy. There is no inherent reason to believe that adolescent females would have different pharmacokinetic characteristic compared to adult females. These apparent differences are possibly related to limitations associated with cross study comparisons and study design differences between the two studies.
- Since the unbound concentrations of LNG were not measured in this study, it is unclear whether the more physiologically relevant unbound concentrations of LNG are different between the adolescent and adult female groups.
- Johansson *et al* found a good correlation between baseline SHBG levels and LNG concentrations (C_{max}) when two doses of 0.75 mg LNG tablet were administered at either 12- (r = 0.79) or 24-hour time intervals (r = 0.86) (Johansson *et al* 2002, Human Reproduction 17:1472-6). However, SHBG levels were not measured in Studies PK-001 and PK-002 to make a comparison.

Figure 1. LNG Plasma Concentration vs. Time after a Single 0.75 mg Oral Dose (Studies PK-001 and PK-002).

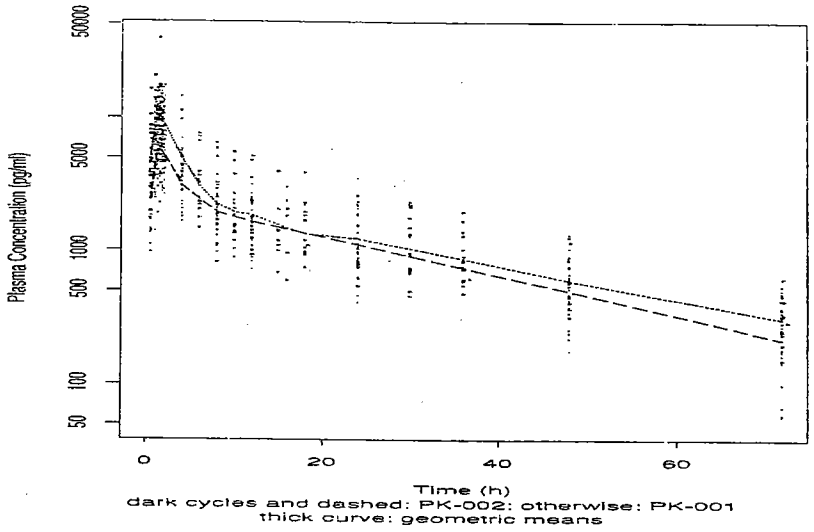
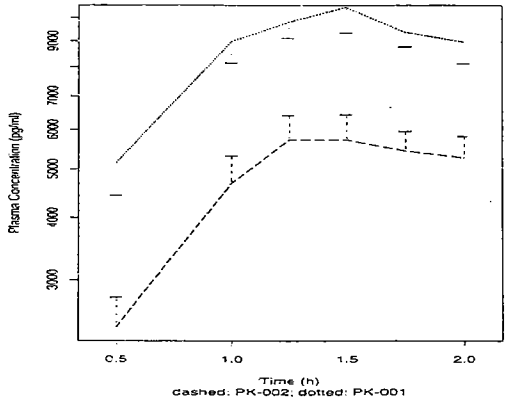
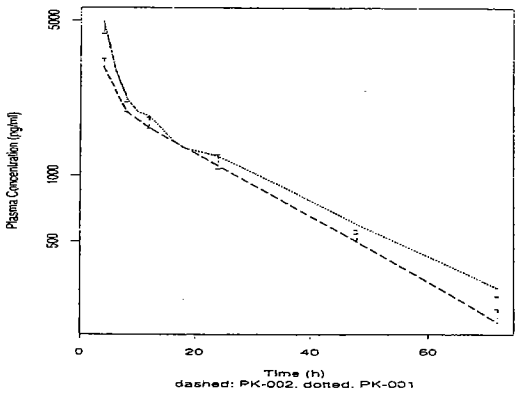


Figure 2. LNG Plasma Concentration vs. Time after a Single 0.75 mg Oral Dose from 0 – 2 hrs (Studies PK-001 and PK-002).

(A) Time: 0 – 2 hrs



(B) Time: 4 – 72 hrs



-Geometric Mean and SE

Effect of Race

No formal studies have evaluated the effect of race. However, clinical trials demonstrated a higher pregnancy rate in the Chinese population with both Plan B and the Yuzpe regimen (another form of emergency contraception consisting of two doses of ethinyl estradiol 0.1 mg + LNG 0.5 mg). The reason for this apparent increase in the pregnancy rate of emergency contraceptives in Chinese women is unknown (Plan B Package Insert). The literature data have no racial and ethnic differences observed in other studies.

In Study PK-001 (n=16), only one Asian Pacific adult female subject was studied. The AUC and C_{max} values were 62511 pg*hr/mL and 9448 pg/mL, respectively. The observed AUC was the lowest among all subjects studied. Dr. Parekh stated in her review that it is unknown whether this finding can be generalized for all Asian population and whether this can be the potential cause of higher pregnancy rate in this ethnic group (NDA 21-045 review).

Table 4. Mean pharmacokinetic parameters of LNG following a single oral dose of 0.75 mg LNG tablet (arithmetic mean ±SD, range)

	PK-001 (Adult females)			PK-002 (Adolescent females)				Adult females	Adult females	Adult females
								Landgren et al	He et al	Shi et al
	Plan B			Plan B				Gedeon Richter	Postinor	Gedeon Richter
Mean±SD (range)	Caucasian (U.S.) (n=9)	Black (U.S) (n=6)	Asian (U.S.) (n=1)	Black (U.S.) (n=12)	Multiracial (U.S.) (n=5)	Latina (U.S.) (n=4)	Asian (U.S.) (n=1)	Swedish (Sweden) (n=10)	Chinese (China) (n=10)	Chinese (China) (n=6)
C_{max} (ng/mL)	15.9±9.3 (6.7-39)	12.2±4.9 (7.4-20.5)	9.4	7.0±3.2 (3.8-12.9)	9.0±5.7 (4.1-16.8)	7.6±3.8 (4.1-12.9)	5.5	16nmol/L	11.2±3.4 (8.1-18.4)	8.6±2.0 (5.3-10.1)
T_{max} (hr)	1.8±0.9 (1-4)	1.4±0.4 (1-1.8)	1.3	1.4±0.3 (1-1.8)	1.9±1.2 (1-4)	1.6±0.5 (1-2)	1.3	2	1.9±0.6 (1-2.7)	3.3±1.0 (2-4)
AUC_{inf} (ng*hr/mL)	129±51 (81-219)	119.3±48 (65-176)	62.5	93.8±33.8 (60-184)	114.4±70 (44-224)	80.2±49.2 (47-151)	61.1	NR	124±42.8 (66.8-177)	116.2±41 (67-160)
Assay	GC/MS/MS							Radioimmunoassay		

NR: Not reported, 1 nmol/L = 0.312 ng/mL

Landgren *et al* 1989 Contraception 39:275-89, He C *et al* 1990 Contraception 41:557-67, Shi *et al* 1988 Contraception 37:359-69

Effect of Body Mass Index
In Study PK-002, the mean BMI of 22 healthy adolescent female subjects was 23.8 ± 3.1 (range, 18.5 – 28.9). In Study PK-001, the mean BMI of 16 healthy female subjects was 23.7 ± 2.4 (range, 19.26 – 26.45).

Johansson *et al* reported that there was no correlation between BMI and LNG concentrations (C_{max}) achieved with any of the three regimens (one single 1.5 mg dose of LNG or two separate administrations of 0.75 mg LNG at either 12- or 24-hour time intervals) (Johansson *et al* 2002, Human Reproduction 17:1472-6).

D. Extrinsic Factors

Drug Interactions
No formal studies of drug-drug interactions were conducted.

E. General Biopharmaceutics
The drug substance and drug product proposed for use in the OTC version of Plan B is manufactured by Gedeon Richter, Ltd. of Budapest, Hungary, the manufacturer of the prescription-only product. The formulation and dosage remain the same as the prescription product.

Effect of Food
No formal study of the effect of food on the absorption of LNG has been undertaken.

F. Analytical Methods
The same analytical laboratory using the same assay method was used to determine LNG concentrations in Studies PK-001 and PK-002.

PK-002: Plasma concentrations of LNG were determined by MDS Pharma Services (formerly Phoenix International Life Sciences Inc.) using a GC/MS/MS analytical method. The lower limit of assay quantitation was 0.142 ng/mL, the upper limit of assay quantitation was 7,712.0 pg/mL. Intra-batch and inter-day variability was less than 15%.

PK-001: Calibration standards over the range of 50.15 to 8024.00 pg/mL were linear with correlation coefficients of 0.9953 for linear regression analyses. Between-batch precision (%CV) and accuracy (%Nominal) for the QC samples (49.95, 149.85, 2497.50, and 6393.60 pg/mL) ranged from 2.9 % to 11.1 % and 100.4 % to 113.3 %, respectively. Within batch precision (%CV) and accuracy (%Nominal) for the QC samples ranged from 2.8 % to 7.4 % and 97.4 % to 113.7 %, respectively.

G. Labeling

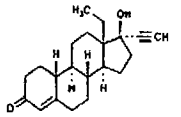
Plan B Package Insert

Plan B® (levonorgestrel) tablets, 0.75 mg

Plan B® is intended to prevent pregnancy after known or suspected contraceptive failure or unprotected intercourse. Emergency contraceptive pills (like all oral contraceptives) do not protect against infection with HIV (the virus that causes AIDS) and other sexually transmitted diseases.

DESCRIPTION

Emergency contraceptive tablet. Each Plan B® 100 mg tablet contains 0.75 mg of a single active steroid ingredient levonorgestrel (18,19-Dinorpregn-4-en-20-yn-3-one,13-ethyl-17-hydroxy-, (17α)-), a totally synthetic progestogen. The inactive ingredients present are colloidal silicon dioxide, potato starch, pregelatinized starch, talc, croscarmellose, and lactose monohydrate. Levonorgestrel has a molecular weight of 312.45, and the following structural and molecular formulas:



$C_{21}H_{28}O_2$

CLINICAL PHARMACOLOGY

Emergency contraceptives are not effective if the woman is already pregnant. Plan B® is believed to act as an emergency contraceptive principally by preventing ovulation or fertilization (by altering tubal transport of sperm and/or ova). In addition, it may inhibit implantation (by altering the endometrium). It is not effective once the process of implantation has begun.

Pharmacokinetics

Absorption

No specific investigation of the absolute bioavailability of Plan B® in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability about 100%) and is not subject to first pass metabolism.

After a single dose of Plan B® (0.75 mg) administered to 16 women under fasting conditions, maximum serum concentrations of levonorgestrel are 14.1 ± 7.7 ng/mL (mean ± SD) at an average of 1.7 ± 0.7 hours. No formal study of the effect of food on the absorption of levonorgestrel has been undertaken.

Table 1 Pharmacokinetic Parameter Values Following Single Dose Administration of Plan B® (Levonorgestrel 0.75 mg) to Healthy Female Volunteers

N	Mean (± S.D.)					
	C_{max} (ng/mL)	T_{max} (h)	CL (L/h)	V_d (L)	$T_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·mL/h)
16	14.1 ± 7.7	1.6 ± 0.7	7.7 ± 2.7	260.8	24.4 ± 5.3	123.1 ± 70.1

Distribution

Levonorgestrel in serum is primarily protein bound. Approximately 50% is bound to albumin and 47.5% is bound to sex hormone binding globulin (SHBG).

Metabolism

Following a single oral dosage, levonorgestrel does not appear to be extensively metabolized by the liver. The primary metabolites are 3α,5β- and 3α,5α-tetrahydrolevonorgestrel with 16β-hydroxylevonorgestrel also identified. Together, these account for less than 10% of parent plasma levels. Urinary metabolites having lost the 13- and 18β-ethyl moieties have also been identified. Small amounts of the metabolites are present in plasma as sulfate and glucuronide conjugates.

Excretion

The elimination half-life of levonorgestrel following single dose administration as Plan B® (0.75 mg) is 24.4 ± 5.3 hours. Excretion following single dose administration as emergency contraception is unknown, but based on chronic low-dose contraceptive use, levonorgestrel and its metabolites are primarily excreted in the urine with smaller amounts recovered in the feces.

Special Populations

Geriatric

This product is not intended for use in postmenopausal women (age 45 years or older); populations and pharmacokinetic data are not available for this population.

Pediatric

This product is not intended for use in prepubertal (premenarchal) populations and pharmacokinetic data are not available for this population.

Race

No formal studies have evaluated the effect of race. However, clinical trials demonstrated a higher pregnancy rate in the Chinese population with both Plan B® and the Yuzpe regimen (another form of emergency contraception consisting of two doses of ethinyl estradiol (0.1 mg) + levonorgestrel (0.5 mg)). The reason for this apparent increase in the pregnancy rate of emergency contraception in Chinese women is unknown.

Hepatic Insufficiency and Renal Insufficiency

No formal studies have evaluated the effect of hepatic insufficiency or renal insufficiency on the disposition of emergency contraception tablets.

Drug-Drug Interactions

No formal studies of drug-drug interactions were conducted.

INDICATIONS & USAGE

Indication

Plan B® is an emergency contraceptive that can be used to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure. To obtain optimal efficacy, the first tablet should be taken as soon as possible within 72 hours of intercourse. The second tablet must be taken 12 hours later.

Clinical Studies

A double-blind, controlled clinical trial in 1,998 evaluable women compared the efficacy and safety of Plan B® (two 0.75 mg tablets of levonorgestrel taken within 72 hours of intercourse, and one tablet taken 12 hours later) to the Yuzpe regimen dose taken at 0.25 mg ethinyl estradiol and 0.05 mg ethinyl estradiol, taken within 72 hours of intercourse, and two tablets taken 12 hours later). Plan B® was at least as effective as the Yuzpe regimen in preventing pregnancy. After a single act of intercourse, the expected pregnancy rate of 8% (with no contraception) was reduced to approximately 1% with Plan B®. Thus, Plan B® reduced the expected number of pregnancies by 85%.

Emergency contraceptives are not as effective as routine contraception since their failure rate, which has been based on single use, would accumulate over time with repeated use (see Warnings). See Table 2 below:

Table 2 Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception, and the Percentage Continuing Use at the End of the First Year- United States

	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year
Method (1)	Typical Use (2)	Perfect Use (3)	
Chance[4]	85	15	60
Spermicide[5]	26	6	40
Periodic Abstinence	25		63
Calendar		9	
Ovulation Method		3	
Symptom-Thermal[6]		2	
Post-ovulation		1	
Withdrawal	19	4	
Cap[7]			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragm[7]	20	6	56
Condom[8]			
Female (Reality)	21	5	56
Male	14	3	36
Oral Contraceptives	5		71
Progestin Only		0.5	
Combined		0.1	
IUD			
Progestasert	2.0	1.5	81
Copper T 380A	0.8	0.6	78
LNG	0.1	0.1	81
Depo-Provera	0.3	0.3	
Norplant and Norplant-2	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.10	100

Emergency Contraception Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.

Lactational Amenorrhea Method: LAM is a highly effective temporary method of contraception.[9]

1 Among typical couples who initiate use of a method (not necessarily for the first time) who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

2 Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly) the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

3 [illegible]

4 [illegible]

[illegible]

[illegible]

[illegible]

5 [illegible]

6 [illegible]

[illegible]

CONTRAINDICATIONS

[illegible]

- [illegible]
- [illegible]
- [illegible]

WARNINGS

Plan B® is not recommended for routine use as a contraceptive.

Plan B® is not effective in terminating an existing pregnancy.

Effects on Menses

[illegible]

Ectopic Pregnancy

[illegible]

PRECAUTIONS

Pregnancy

[illegible]

STD/HIV

[illegible]

Physical Examination and Follow-up

[illegible]

Carbohydrate Metabolism

[illegible]

Drug Interactions

[illegible]

Nursing Mothers

[illegible]

Pediatric Use

[illegible]

Fertility Following Discontinuation

[illegible] and long-term contraception

ADVERSE REACTIONS

[illegible]

Table 3 Adverse Events in ≥ 5% of Women, by % Frequency

Most Common Adverse Events	Plan B® Levonorgestrel N=977 (%)
Nausea	23.1
Abdominal Pain	17.6
Fatigue	16.9
Headache	16.8
Heavier Menstrual Bleeding	13.8
Lighter Menstrual Bleeding	12.5
Dizziness	11.2
Breast Tenderness	10.7
Other complaints	9.7
Vomiting	5.6
Diarrhea	5.0

[illegible]

- [illegible]
- [illegible]

DRUG ABUSE AND DEPENDENCE

[illegible]

OVERDOSAGE

[illegible]

DOSAGE AND ADMINISTRATION

[illegible]

HOW SUPPLIED

[illegible]

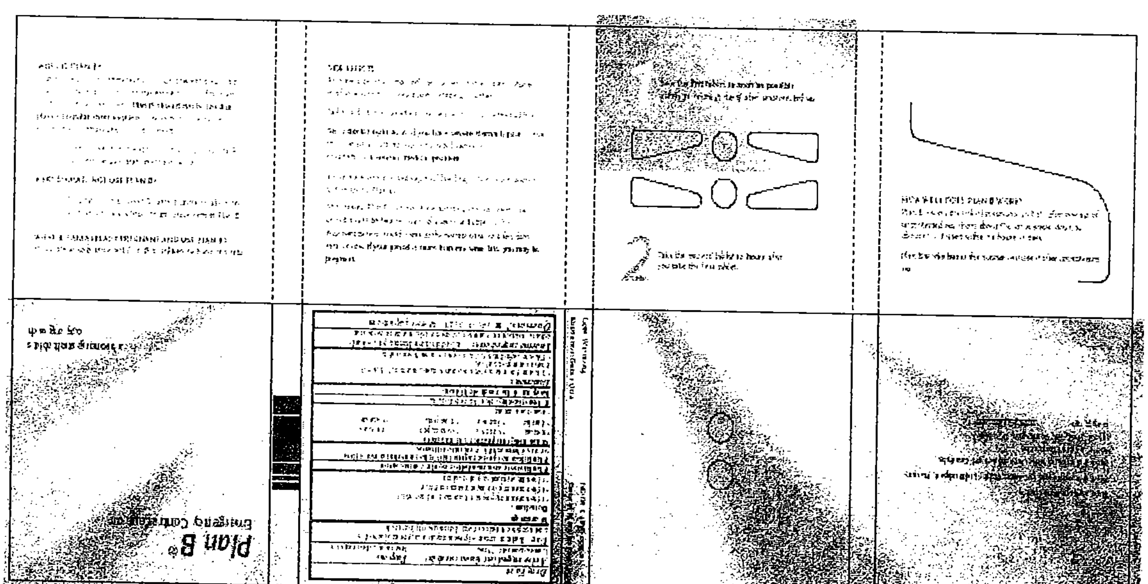
[illegible]

[illegible]

[illegible]

Rx Only

Proposed Commercial Label



IV. Appendix

A. Individual Study Review
B. Cover Sheet and OCPB Filing/Review Form

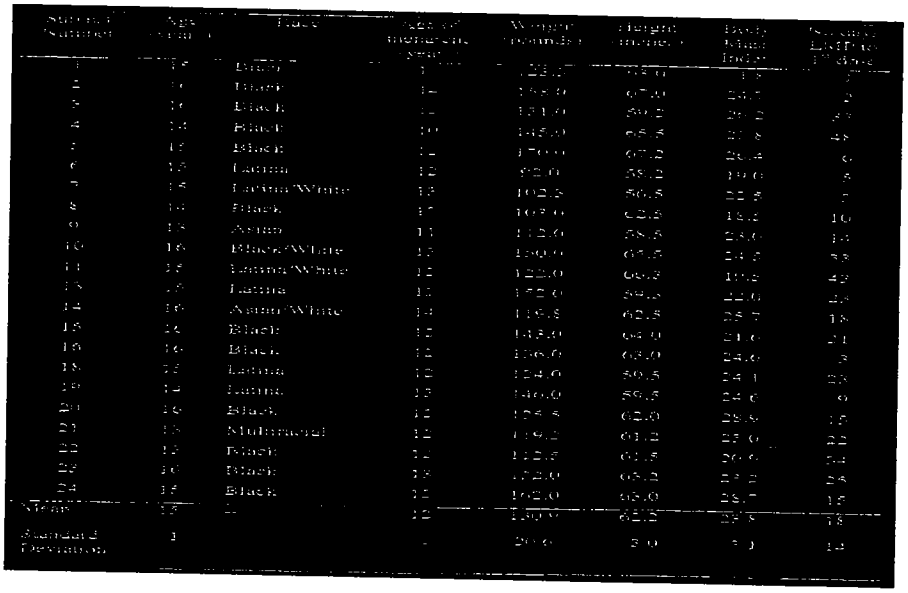
A. Individual Study Review

PK-002: "An Open-Label Pharmacokinetic Study of Plan B Emergency Contraception in a Healthy Female Pediatric Population"

A prospective, single-period, single-center, open-label pharmacokinetic study was conducted to determine the pharmacokinetics of LNG following oral administration of a single 0.75 mg LNG tablet (Plan B) to healthy adolescent females aged 12 to 16 years. A secondary objective was to compare the pharmacokinetic values of LNG in healthy adolescent females to those previously determined in healthy adult females following the administration of a single 0.75 mg LNG tablet (PK-001).

Healthy adolescent female subjects were instructed to fast for at least 4 hours before they report to the study site. They were administered orally a single Plan B 0.75 mg LNG tablet (with 240 mL water) approximately 4 pm - 7 pm to accommodate subjects' school schedules. Blood samples were obtained at pre-dose, and at 0.5, 1, 1.25, 1.5, 1.75, 2, 4, 8, 10, 12, 24, 48, and 72 hours post-dose. Subjects continued to fast for at least 3 hours post-dose.

Table 5. The demographic and other baseline characteristics of 22 healthy adolescent females.



A total of 23 subjects were enrolled and 22 of them completed the study. One subject could not complete the study because the indwelling intravenous catheter for blood draws could not be inserted. She did not receive medication.

- The mean age of 22 subjects was 15 ± 1 yrs (range, 13 to 16 yrs).
- The mean body mass index (BMI) was 23.8 ± 3.1 (range, 18.5 – 28.9).
- Their age of menarche ranged from 10 to 14 yrs with a mean age of menarche of 12 ± 1 yrs.

- The adolescents were predominantly black (54%), multiracial (23%) or Latina (18%) in comparison with the adults who were predominantly white (56%) and black (38%).

Table 6. LNG pharmacokinetic parameters of 22 healthy adolescent females.

Subject Number	t_{max} (h)	C_{max} (pg/mL)	λ_z (h^{-1})	$t_{1/2}$ (h)	$AUC_{t_{max}}$ (pg•h/mL)	AUC_{inf} (pg•h/mL)	CL/F (mL/min)	V/F (L)
1	1.25	4005	0.0419	16.6	76551	80717	154.9	221.9
2	1.00	4781	0.0252	29.9	66071	78575	159.1	412.1
3	2.00	8764	0.0194	35.8	82775	107850	115.9	359.1
4	1.50	7218	0.0334	20.7	66525	73800	169.4	304.2
5	1.00	6750	0.0232	29.9	55295	60234	207.5	374.6
6	1.50	12913	0.0596	17.5	142605	150821	82.9	125.6
7	1.50	10818	0.0404	17.2	211336	224374	55.7	82.8
8	1.25	10254	0.0602	11.5	78220	79206	157.8	157.2
9	1.25	5498	0.0586	18.0	57349	61140	204.4	318.1
10	4.00	4052	0.0266	26.0	83037	96038	130.2	293.5
11	1.25	4644	0.0465	14.9	42662	44129	259.9	365.5
13	1.00	6581	0.0217	31.9	68815	76695	169.0	450.3
14	1.00	13395	0.0365	19.1	125405	135438	92.9	152.4
15	1.75	6254	0.0276	25.1	68840	77431	161.4	350.9
16	1.50	5145	0.0256	27.0	71022	82223	152.0	355.9
18	2.00	6510	0.0292	23.7	45104	46550	268.5	552.0
19	2.00	4088	0.0229	30.3	39912	40038	265.0	703.3
20	1.75	12670	0.0327	21.2	166799	183517	68.1	125.0
21	1.75	5931	0.0564	12.3	70967	71999	145.0	184.7
22	1.00	12864	0.0365	19.0	114228	121685	102.7	168.8
23	1.00	5212	0.0386	18.0	104712	112186	111.4	173.2
24	1.25	4655	0.0215	32.3	50411	66627	182.1	508.6
G.M.	1.43	6715	0.0326	21.2	77798	86140	145.1	260.8
C.V.(%)	38.7	45.8	31.0	31.0	48.7	42.9	42.9	55.8

G.M.: geometric mean C.V.: coefficient of variation

Table 7. Statistical summary of LNG pharmacokinetic parameters in adolescent females (Study PK-002) and adult females (PK-001).

Parameter		Adolescent G.M.	Adolescent C.V. (%)	Adult G.M.	Adult C.V. (%)	p-Value	Ratio (90% C.I.)
t_{max}	(h)	1.43	38.7	1.82	37.2	0.604	0.82 (0.55, 1.23)
C_{max}	(pg/mL)	6715	45.8	12764	43.7	0.0001*	0.53 (0.41, 0.68)
λ_z	(h^{-1})	0.0326	31.0	0.0291	22.6	0.213	1.12 (0.94, 1.33)
$t_{1/2}$	(h)	21.2	31.0	23.9	22.6	0.213	0.89 (0.75, 1.04)
$AUC_{t_{max}}$	(pg•h/mL)	77798	48.7	100410	42.5	0.075	0.77 (0.61, 0.98)
AUC_{inf}	(pg•h/mL)	86140	42.9	112502	40.0	0.059	0.77 (0.61, 0.96)
CL/F	(mL/min)	145.1	42.9	111.1	40.0	0.059	1.31 (1.04, 1.65)
V/F	(L)	260.8	55.8	229.4	55.6	0.415	1.18 (0.85, 1.64)

G.M.: geometric mean C.V.: coefficient of variation
Ratio: adolescent/adult of geometric means C.I.: confidence interval
*: statistically significant

- In adolescents, the geometric mean LNG C_{max} was 6,715 pg/mL (CV 45.8%) and the mean AUC_{inf} was 86,140 pg*hr/mL (CV 42.9%).
- In adults, the geometric mean LNG C_{max} was 12,764 pg/mL (CV 43.7%) and the mean AUC_{inf} was 112,502 pg*hr/mL (CV 40.0%).
- There was a statistically significant difference between the adolescent and adult females with respect to C_{max} (a mean ratio of adolescents/adults = 0.53, 90% CI of 0.41, 0.68).
- The difference between the two groups with respect to AUC_{inf} was borderline significant with a mean ratio (adolescents/adults) of 0.77 (90% CI of 0.61, 0.96).

Figure 3. LNG plasma concentration vs. time after a single 0.75 mg Plan B oral dose from 0 – 72 hrs (Studies PK-001 and PK-002).

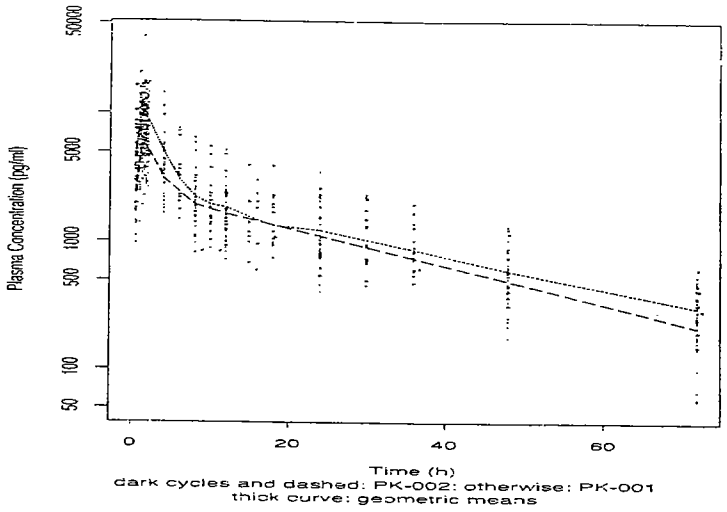
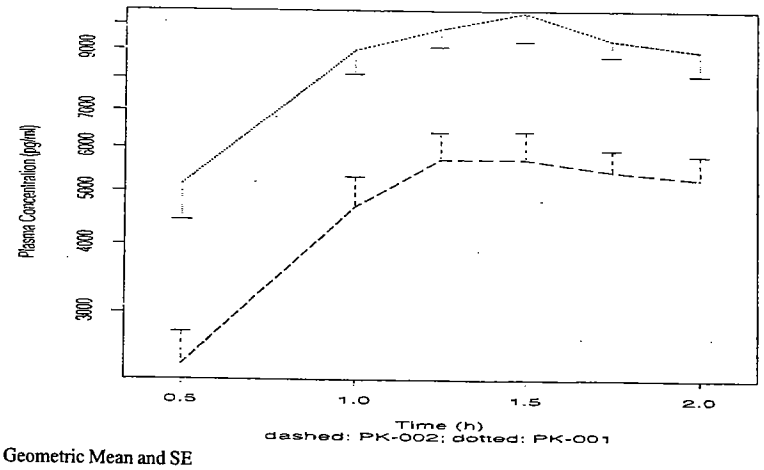
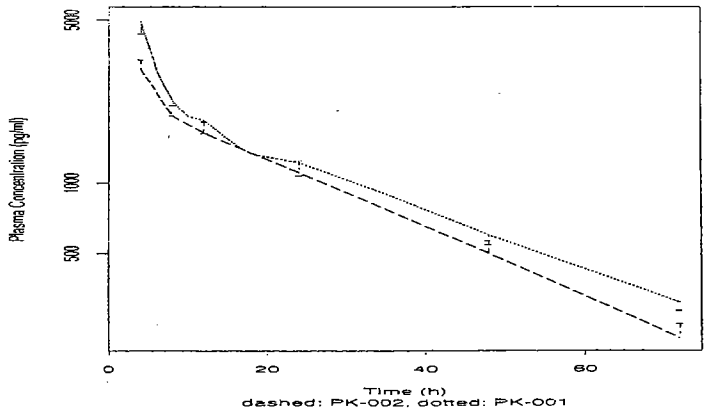


Figure 4. LNG plasma concentration vs. time after a single 0.75 mg Plan B oral dose from 0 – 2 hrs (Studies PK-001 and PK-002).



Geometric Mean and SE

Figure 5. LNG plasma concentration vs. time after a single 0.75 mg Plan B oral dose from 4 – 72 hrs (Studies PK-001 and PK-002).

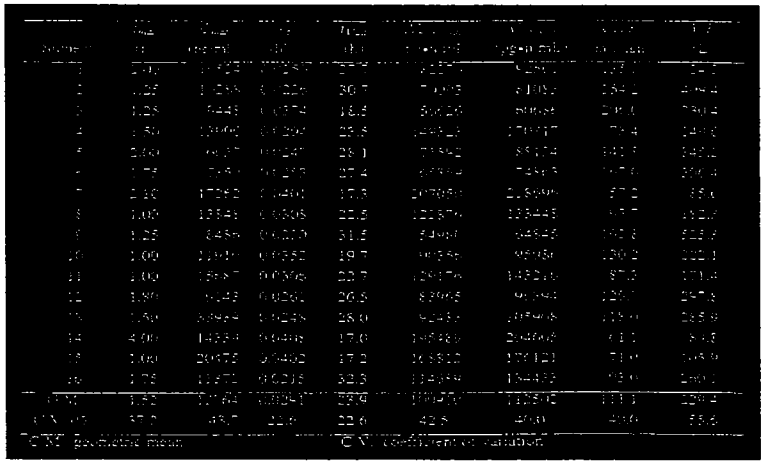


-Geometric Mean and SE

Study WCC-PK-001 (previously submitted to NDA 21-045): "A Two-Period, Crossover Study of the Relative Bioavailability of Levonorgestrel 0.75 mg Tablets Administered Orally to Fasting Female Volunteers"

A randomized, single-center, two-period, crossover study was conducted in 16 healthy adult females aged 18 to 45 years to investigate the oral bioavailability of Plan B 0.75 mg LNG tablet relative to a suspension of micronized LNG drug substance. The secondary objective was to characterize the pharmacokinetic parameters of the proposed commercial formulation. Subjects received a LNG 0.75 mg tablet (with 240 mL water) and a suspension of micronized LNG drug substance following an overnight fast, separated by a washout of at least one week. Blood samples were obtained at pre-dose, 0.5, 1, 1.25, 1.5, 1.75, 2, 4, 6, 8, 10, 12, 15, 18, 24, 30, 36, 48, and 72 hours post-dose. Plasma samples were analyzed at Phoeniz International Life Sciences Inc. (Montreal) using GC/MS.

Table 8. LNG pharmacokinetic parameters of 16 healthy adult females.



- Note: Subject 13 had a pre-dose LNG concentration of 75 pg/mL.

Table 9. Mean plasma concentrations of 0.75 mg LNG tablet (pg/mL).

	Hours Post Study Drug Dose (N=16)									
Study Statistic	0	0.5	1	1.25	1.5	1.75	2	4	6	8
Mean	4.7	6085.7	9666.3	10177.3	11926.1	9692.7	9638.1	5581.4	3466.5	2657.6
SD	18.8	3735.0	4112.3	2762.2	7926.5	2604.6	3861.0	3509.8	1963.5	1713.1
		10	12	15	18	24	30	36	48	72
Mean		2228.3	2132.8	1669.2	1502.3	1390.8	1182.6	949.7	644.2	525.5
SD		1347.3	1295.6	915.7	847.9	729.5	641.8	441.6	272.6	117.0

Table 10. Mean pharmacokinetic results of 0.75 mg LNG tablets.

Study Statistic	AUC_{0-t} (pg*hr/mL)	AUC_{0-inf} (pg*hr/mL)	Cmax (pg/mL)	Tmax (Hrs)	Half-Life (Hrs)	MRT (Hr)	CL (L/Hr)	VD_β (L)
Mean	111774.5	123113.8	14111.4	1.6	24.4	27.8	7.7	260.0
SD	49162.4	50129.4	7677.2	0.7	5.3	5.2	2.7	129.5

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form+

General Information About the Submission

	Information		Information
NDA Number	21-045	Brand Name	Plan B
OCPB Division (I, II, III)	DPE II	Generic Name	Levonorgestrel
Medical Division	DRUDP	Drug Class	Oral Contraceptive
OCPB Reviewer	Myong-Jin Kim	Indication(s)	Emergency Contraceptive
OCPB Team Leader	Ameeta Parekh	Dosage Form	Tablet
		Dosing Regimen	0.75 mg
Date of Submission	22/April/2003	Route of Administration	Oral
Estimated Due Date of OCPB Review		Sponsor	Women's Capital Corp.
PDUFA Due Date	21/May/2004	Priority Classification	S
Division Due Date	30/January/2004		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling				
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2	2	
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	X			
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				

Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X		9	
Total Number of Studies			**11**	

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-045, HFD-850 (L.Lesko, S.Huang), HFD-580 (D. Davis, S. Monroe), HFD-870 (A. Parekh, H. Malinowski, J. Hunt), CDR (B. Murphy)

CP&B Briefing attendees on December 12, 2003: Drs. D.J.Chatterjee, D. Davis, D. Griebel, J. Hunt, L. Kenna, H.Malinowski, S. Ortiz, and A.Parekh.

Filing Memo

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-045
Compound: Plan B (Levonorgestrel)
Sponsor: Women's Capital Corporation

Date: 06/June/2003
Reviewer: Myong-Jin Kim

Background:
The supplemental drug application of Plan B, NDA 21-045/S-010, was submitted to request for switch to OTC under section 505(b) on April 22, 2003.

New Pharmacokinetic Studies Submitted in sNDA 21-045:

1) PK-002 (UCSF 2002): An open-label PK study of Plan B emergency contraception in a healthy female pediatric population
   - Prospective, single-period, single-center, open-label PK study in young adolescents aged 13 – 16 years (n=22)
   - Study objectives: (1) to determine the PK of LNG following oral administration of a single 0.75 mg tablet to healthy young adolescent females, (2) to compare the systemic exposure between healthy adolescent females and adult females studied in WCC-PK-001 (Kook 2002)
   - Blood samples were collected at 0 (pre-dose), 0.5, 1.25, 1.5, 1.75, 2, 4, 8, 10, 12, 24, 48, and 72 hours post-dose
   - The same analytical laboratory using the same assay method in both studies WCC-PK-001 and UCSF 2002

2) PK study of different dosing regimens of LNG for emergency contraception in healthy women (Johansson 2002)
   - Single-center, open-label, cross-over PK study to determine the PK of the currently accepted LNG in emergency contraception regimen consisting of two doses of 0.75 mg LNG (Norlevo: HRA Pharma, Paris France) given 12 h apart and the PK associated with two additional regimens
   - Five non-breastfeeding healthy women 18-45 years of age participated in the three arms of the study with a washout period between treatments of 27-28 d.
   - Treatment A: two doses of 0.75 mg LNG given 12 h apart
   - Treatment B: two doses of 0.75 mg LNG given 24 h apart
   - Treatment C: a single dose of 1.5 mg LNG (two 0.75 mg tablets)
   - Blood samples were collected 0 (pre-dose), 1, 2, 4, 8, and 12 h after each dose; samples were then taken every 12 h on Days 2- 4, and every 24 h on Days 5 -10.
   - SHBG was measured.

3) The PK of 750 μg LNG following administration of one single or two doses at 12- or 24-h interval (Tremblay 2001)

- Open-label, observer-blind, randomized study with three parallel groups and three treatments
- Twenty four healthy white women 18-26 years of age were enrolled to determine the plasma levels of LNG following a single Norvelo®/Vikela® (Laboratoire HRA Pharma, Paris France) tablet administration and following a second administration 12 or 24 h after the first dose.
- Group A: one tablet of 0.75 mg LNG and another tablet 12 h later (n=8)
- Group B: one tablet of 0.75 mg LNG (n=8)
- Group C: one tablet of 0.75 mg LNG and another tablet 24 h later (n=8)
- Blood samples were collected 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, and 36 h post-dose.

PK Studies Resubmitted from NDA 21-045:
(WCC-PK-001, He 1990, Landgren 1989, Shi 1988):

1) WCC-PK-001: A two period, crossover study of the relative BA of LNG 0.75 mg tablets administered orally to fasting female volunteers (WCC-PK-001, Kook 2002)
   - Study objectives: (1) to compare the BA of LNG 0.75 mg tablets relative to a suspension of micronized LNG drug substance, (2) to characterize the PK of the proposed commercial formulation
   - Sixteen healthy adult women were enrolled. Each subject received both formulations separated by a washout period of at least one week.
   - Blood samples were collected 72 h post-dose
   - Analytical Report: previously submitted in original NDA 21-045

2) Comparative cross-over PK study on two types of postcoital contraceptive tablets containing LNG (He 1990)
   - A randomized, double-blind, multicenter, crossover trial of the Gedeon Richter, Ltd. Formulation (Postinor) and an experimental Chinese formulation of LNG 0.75 mg
   - Ten women took both products, one on Day 3 of their cycle and one on Day 7.
   - Blood samples were collected over a 24-h period following each drug administration.

3) The effect of LNG administered in large doses at different stages of the cycle on ovarian function and endometrial morphology (Landgren 1989)
   - Single-dose study to evaluate a PK/PD into the mechanism of action of LNG when given for 4 days in different phases of the menstrual cycle.
   - Study A: 10 women were administered LNG 0.75 mg between Days 2-6 of their cycle
   - Study B: 72 women were assigned to four treatment groups. LNG 0.75 mg was given orally for 4 days in the follicular phase, periovulatory period, or luteal phase.

4) PK study of LNG used as a postcoital agent (Shi 1988)
   - A multiple-dose study to evaluate the PK/PD of LNG during the periovulatory phase of the menstrual cycle in 6 healthy young women (27-35 years old). LNG 0.75 mg was given daily for 7 days.

5) LNG: Clinical Pharmacokinetics (Fotherby 1995)
   - Literature review.

Literature References on PK Studies

1) SD PK of 0.75 mg LNG
   - WCC-PK-001, Kook 2002, UCSF 2002, Tremblay 2001, He 1990, Landgren 1989, Shi 1988
2) SD PK of 1.5 mg LNG
   - Johansson 2002
3) MD PK of 0.75 mg LNG
   - Landgren 1989 (0.75 mg LNG QD x 4 d); Johansson 2002 (two 0.75 mg doses given both 12 and 24 h apart); Tremblay 2001 (two 0.75 mg doses given both 12 and 24 h apart)

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II find that the Human Pharmacokinetics and Bioavailability section for sNDA 21-045 is fileable.

_____ _____

Myong-Jin Kim, Pharm.D. Date

_____ _____

Ameeta Parekh, Ph.D., Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Myong-Jin Kim
3/12/04 03:22:46 PM
PHARMACOLOGIST

Ameeta Parekh
3/12/04 03:25:29 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-045	Brand Name	Plan B
OCPB Division (I, II, III)	DPE II	Generic Name	Levonorgestrel
Medical Division	DRUDP	Drug Class	Contraceptive
OCPB Reviewer	Myong-Jin Kim	Indication(s)	Emergency Contraceptive
OCPB Team Leader	Ameeta Parekh	Dosage Form	Tablet
		Dosing Regimen	0.75 mg
Date of Submission	22/April/2003	Route of Administration	Oral
Estimated Due Date of OCPB Review		Sponsor	Women's Capital Corp.
PDUFA Due Date	20/February/2004	Priority Classification	S
Division Due Date	30/January/2004		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling				
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	X			
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	X			
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				

II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X			
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies				

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-045, HFD-850 (L.Lesko, S.Huang), HFD-580 (D. Davis, S. Monroe), HFD-870 (A. Parekh, H. Malinowski, J. Hunt), CDR (B. Murphy)
CP&B Briefing attendees on: Drs.

Filing Memo

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-045
Compound: Plan B (Levonorgestrel)
Sponsor: Women's Capital Corporation

Date: 06/June/2003
Reviewer: Myong-Jin Kim

Background:
Plan B® (levonorgestrel, LNG, 0.75 mg tablet, NDA 21-045) was approved by the FDA on July 28, 1999 as a prescription product for emergency contraception in all women of reproductive age. This product is used as a 2-tablet regimen with the first tablet to be taken as soon as possible within 72 hours after unprotected sexual intercourse and the second tablet to be taken 12 hours later. A third dose is recommended if vomiting occurs within 4 hours after either required dose. Women's Capital Corporation (WCC) submitted the Supplement to this approved NDA to request a prescription to over-the-counter (Rx-to-OTC) switch on April 22, 2003. The dosage and instructions for use remain the same.

New Pharmacokinetic Studies Submitted to sNDA 21-045:

1) PK-002 (UCSF 2002): An open-label PK study of Plan B emergency contraception in a healthy female pediatric population
   - Prospective, single-period, single-center, open-label PK study in young adolescents aged 13 – 16 years (n=22)
   - Study objectives: (1) to determine the PK of LNG following oral administration of a single 0.75 mg tablet to healthy young adolescent females, (2) to compare the systemic exposure between healthy adolescent females and adult females studied in WCC-PK-001 (Kook *et al* 2002, Contraception 66:73-6)
   - Blood samples were collected at 0 (pre-dose), 0.5, 1.25, 1.5, 1.75, 2, 4, 8, 10, 12, 24, 48, and 72 hours post-dose
   - The same analytical laboratory using the same assay method in both studies WCC-PK-001 and UCSF 2002

2) PK study of different dosing regimens of LNG for emergency contraception in healthy women (Johansson *et al* 2002, Human Reproduction 17:1472-6)
   - Single-center, open-label, cross-over PK study to determine the PK of the currently accepted LNG in emergency contraception regimen consisting of two doses of 0.75 mg LNG (Norlevo: HRA Pharma, Paris France) given 12 h apart and the PK associated with two additional regimens
   - Five non-breastfeeding healthy women 18-45 years of age participated in the three arms of the study with a washout period between treatments of 27-28 d.
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   - Treatment C: a single dose of 1.5 mg LNG (two 0.75 mg tablets)

- Blood samples were collected 0 (pre-dose), 1, 2, 4, 8, and 12 h after each dose; samples were then taken every 12 h on Days 2- 4, and every 24 h on Days 5 -10.
- SHBG was measured.

3) The PK of 750 µg LNG following administration of one single or two doses at 12- or 24-h interval (Tremblay *et al* 2001, Contraception 64:327-31)
   - Open-label, observer-blind, randomized study with three parallel groups and three treatments
   - Twenty four healthy white women 18-26 years of age were enrolled to determine the plasma levels of LNG following a single Norvelo®/Vikela® (Laboratoire HRA Pharma, Paris France) tablet administration and following a second administration 12 or 24 h after the first dose.
   - Group A: one tablet of 0.75 mg LNG and another tablet 12 h later (n=8)
   - Group B: one tablet of 0.75 mg LNG (n=8)
   - Group C: one tablet of 0.75 mg LNG and another tablet 24 h later (n=8)
   - Blood samples were collected 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, and 36 h post-dose.

PK Studies Resubmitted from NDA 21-045:
(WCC-PK-001, He *et al* 1990, Contraception 41:557-67, Landgren *et al* 1989, Contraception 39:275-89, Shi *et al* 1988, Contraception 37:359-69):

1) WCC-PK-001: A two period, crossover study of the relative BA of LNG 0.75 mg tablets administered orally to fasting female volunteers (WCC-PK-001, Kook 2002)
   - Study objectives: (1) to compare the BA of LNG 0.75 mg tablets relative to a suspension of micronized LNG drug substance, (2) to characterize the PK of the proposed commercial formulation
   - Sixteen healthy adult women were enrolled. Each subject received both formulations separated by a washout period of at least one week.
   - Blood samples were collected 72 h post-dose
   - Analytical Report: previously submitted in original NDA 21-045

2) Comparative cross-over PK study on two types of postcoital contraceptive tablets containing LNG (He 1990)
   - A randomized, double-blind, multicenter, crossover trial of the Gedeon Richter, Ltd. Formulation (Postinor) and an experimental Chinese formulation of LNG 0.75 mg
   - Ten women took both products, one on Day 3 of their cycle and one on Day 7.
   - Blood samples were collected over a 24-h period following each drug administration.

3) The effect of LNG administered in large doses at different stages of the cycle on ovarian function and endometrial morphology (Landgren 1989)
   - Single-dose study to evaluate a PK/PD into the mechanism of action of LNG when given for 4 days in different phases of the menstrual cycle.
   - Study A: 10 women were administered LNG 0.75 mg between Days 2-6 of their cycle
   - Study B: 72 women were assigned to four treatment groups. LNG 0.75 mg was given orally for 4 days in the follicular phase, periovulatory period, or luteal phase.

4) PK study of LNG used as a postcoital agent (Shi 1988)

- A multiple-dose study to evaluate the PK/PD of LNG during the periovulatory phase of the menstrual cycle in 6 healthy young women (27-35 years old). LNG 0.75 mg was given daily for 7 days.

5) LNG: Clinical Pharmacokinetics (Fotherby 1995, Clin Pharmacokinet 28:203-15)
   - Literature review.

Literature References on PK Studies

1) SD PK of 0.75 mg LNG
   - WCC-PK-001, Kook 2002, UCSF 2002, Tremblay 2001, He 1990, Landgren 1989, Shi 1988
2) SD PK of 1.5 mg LNG
   - Johansson 2002
3) MD PK of 0.75 mg LNG
   - Landgren 1989 (0.75 mg LNG QD x 4 d); Johansson 2002 (two 0.75 mg doses given both 12 and 24 h apart); Tremblay 2001 (two 0.75 mg doses given both 12 and 24 h apart)

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II find that the Human Pharmacokinetics and Bioavailability section for sNDA 21-045 is fileable.

Myong-Jin Kim, Pharm.D. _____ Date

Ameeta Parekh, Ph.D., Team Leader _____ Date