CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21045

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUL 20 1999

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA 21-045

Drug/Drug Product: PLAN B, levonorgestrel 0.75 mg oral tablets

Indication: Emergency Contraceptive

Date of Application: 1/29/99

Classification: Priority (3P)

Sponsor: Women's Capital Corporation (WCC)

Reviewer: Ameeta Parekh, Ph.D.

SYNOPSIS:

Women's Capital Corporation (WCC) has submitted the NDA 21-045 for levonorgestrel (LNG) 0.75 mg tablets, in response to the FDA's announcement (62 Federal Register, 8610, February 25, 1997) for applications from industry for new products to meet the need of emergency postcoital contraception that may be used to prevent unwanted pregnancies. This oral contraceptive (OC) product is intended to be used as a 2 tablet regimen, with the first 0.75 mg tablet to be taken within 72 hours after unprotected sex and the next 0.75 mg tablet to be taken 12 hours later (PLAN B). LNG has a long history of use in U.S. as a chronic low dose contraceptive, either as a single entity (e.g. implantable Norplant or OC Ovrette) or in combination with estrogens in OC pills.

The Human Pharmacokinetics and Biopharmaceutics section of the NDA provides data from a relative bioavailability study comparing a suspension formulation to the to-be-marketed formulation of Plan B. Sponsor has also provided published literature reports on clinical pharmacokinetics and review articles addressing potential for drug-drug interactions. Well designed studies to assess the influence of hepatic, renal, ethnic differences and age, on pharmacokinetics of LNG have not been evaluated. In-vitro dissolution has been characterized for PLAN B and the sponsor has proposed a method and specification for quality control of the final product.

LNG binds to albumin (50%) and sex hormone binding globulin, SHBG, (47.5%) extensively. The free fraction in plasma is about 2.5% (Fotherby, Clin. Pharmacokin. 28, 3, 1995). After oral administration, LNG is rapidly absorbed and the maximum plasma concentrations (Cmax) are achieved within 1-2 hours (Tmax). Reported studies show minimum first pass and high absolute bioavailability. LNG is a low extraction drug with the reported apparent clearance values ranging from 6-7 L/hr. The apparent volume of distribution is in the range of 100 L.

COMMENTS:

The following general comments (1 and 2) have been conveyed to the sponsor via a telephone conference dated 7/15/99:

1. Information on drug interaction potential is generally useful to assure the efficacy of oral contraceptives. Since PLAN B is indicated for acute indication, knowledge of isozymes responsible for its metabolism could be very useful to determine efficacy implications upon coadministration with other drugs. The sponsor should be encouraged to explore this to address specifically, the drug interaction potential for LNG.

2. It is interesting to note that the only Asian female in the study WCC-PK-001 had low AUCs (62511; range 62511-222143 pg*hours/ml) and Cmax (9448; range 6657-38990 pg/ml) values. Note also that the study conducted by He, et al, Contraception,41,5,1990, compared a Chinese pill to Postinor (Hungarian tablet similar to PLAN B) and showed lower relative bioavailability for the Chinese pill (about 25% for AUC and 100% for Cmax). The pregnancy rates, however, were similar for both products. Given that LNG pharmacokinetics are highly variable, it is not clearly evident that lower concentrations in the Asian population (if in fact this holds) may be the cause of higher pregnancy rates. It could be worthwhile exploring further whether ethnicity is an important covariate for pharmacokinetics of LNG and whether higher doses should be explored in the Asian population.

3. The in-vitro dissolution methodology is acceptable. The specifications should be set as Q % in minutes and this has been conveyed to, and agreed to, by the sponsor in a letter dated 7/13/99.

RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics, DPEII, has reviewed the Section 6 of NDA 21-045 for PLAN B for emergency contraception. The NDA is acceptable from the pharmacokinetics perspective.

/S/ 7/20/99

Ameeta Parekh, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology & Biopharmaceutics

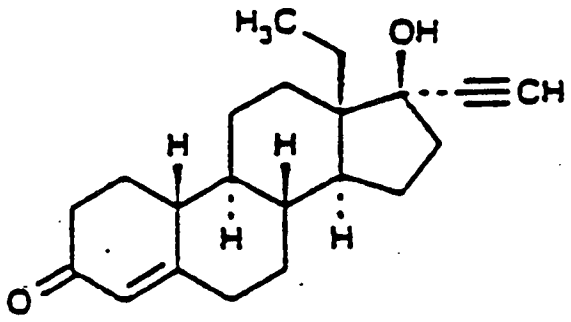
FT Signed by John Hunt /S/ 7/20/99.

OCPB Briefing, 7/15/99 (Dr. Mei-Ling Chen, John Hunt, Dr. Ameeta Parekh)
cc: NDA 21-045, HFD-870 (M.Chen, J. Hunt, A.Parekh), HFD-580 (J.Mercier, D.Davis)
CDR (Barbara Murphy)

BACKGROUND:

LNG, the active isomer of dl-norgestrel, is the active ingredient in the 0.75 mg wet granulation tablets. These are manufactured by
and packaged as 2 blister packs. PLAN B is distributed by Women's Capital Corporation (WCC) in the U.S.

Structure of Levonorgestrel



USAN:	Levonorgestrel
Chemical Name:	18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-(-)-.
Molecular Formula:	$C_{21}H_{28}O_2$
Molecular Weight:	312.45

The Clinical Pharmacology and Biopharmaceutics review is formatted to address the pertinent questions that are generally relevant to this section, as follows:

QUESTIONS:

What is currently available for the indication of emergency contraception (EC) ? Why is NDA 21-045 a priority application ?

Combinations of ethinyl estradiol (EE, 0.1 or 0.12 mg) and levonorgestrel (LNG, 0.5 or 0.6 mg) are believed to be safe and effective for EC use (1996 Advisory Committee decision). Currently, these combinations are used off label for EC indication in the U.S. Preven™ (4 pills each of LNG 0.25mg and EE 0.05mg combination) was approved in 1998 for U.S. market based on the Advisory Committee decision and meta analysis

submitted for the use of this regimen. Currently, this is the only approved product in U.S. for this indication.

The combination products contain estrogen and progestin. The current NDA is a progestin alone product which, according to the sponsor, has reduced side effects due to the absence of estrogen (nausea, vomiting). The safety and efficacy data for the current NDA is derived from well controlled clinical trials specifically for EC.

Is 0.75 mg LNG approved elsewhere in the world for this indication ?

The LNG 0.75 mg tablets are marketed as Postinor™ by since 1980 and available in 34 countries. This is packaged as 4 or 10 tablets for occasional postcoital contraception.

Do clinical safety and efficacy studies support the approval ?

The NDA contains clinical safety and efficacy data from 2 well controlled randomized clinical studies on levonorgestrel for EC. Supporting data is also provided from 3 additional multicenter studies (with 0.75 mg levonorgestrel) and 32 additional single center studies with various doses.

What is the proposed dose and how was this determined ?

This product (PLAN B) will be used as a 2-tablet regimen with the first tablet taken within 72 hours after unprotected sexual intercourse and the next tablet to be taken 12 hours later. A third dose is recommended if vomiting occurs within 4 hours after either required dose.

The dose in the clinical trials was determined based on data accumulated over 3 decades from several countries. Doses of 0.15 to 0.4 mg have been used as OC within 1 hour of infrequent coital act. Doses as high as 1 mg to be used within 8 hours after intercourse have also been reported. Lower LNG doses have been used within 1-8 hours of unprotected intercourse and associated with disruption of menstrual cycles. It is reported that a 30% pregnancy rate was reduced to 1% when the dose of LNG was increased from 0.15mg to 0.75-1mg (Landgren, et.al, Contraception, 39,3,1989). The choice of 0.75 mg dose is based on the established safety and efficacy of its use in many countries.

What is the mechanism of action ?

The mechanism whereby LNG prevents pregnancy as an oral or implantable contraceptive is due to its potent progestin activity. Postcoital administration could theoretically prevent pregnancy by interfering with a number of physiological processes including ovulation, sperm transport through cervical mucus and fallopian tubes, release of pituitary gonadotropins, corpus luteum function, fertilization, embryo transport and implantation. It is not effective once the process of implantation has begun.

Is the clinical trials formulation the same as that to be marketed ?

The proposed commercial product is composed of 2 levonorgestrel 0.75 mg tablets manufactured and packaged by

The same tablet, with minor formulation changes, was used in the pivotal clinical study and most other clinical studies in the NDA. Specifically, tablets produced prior to 1996 (including the formulation used in pivotal clinical trial, WHO/HRP) contained a 5% overage of drug substance and a slightly different ratio of corn starch to potato starch (22:1 vs. 22.5:0.5) compared to current commercial formulation. Note that the total amount of starch remains unchanged. In-vitro dissolution comparison for the 2 formulations show similarity with respect to the dissolution profiles (f2>50). The 5% overage in the clinical trial formulation is not likely to compromise efficacy since the inter- and intra-subject variability reported in the literature for oral LNG is high (2-3 fold differences in clearance between subjects for study WCC-PK-001; 45.3% reported as intra-subject variability, Fotherby; Am.J.Obstet.Gynecol, 163,1,1990. Note that this may not be a true measure of intra-subject variability as estimated by replicate administration).

Are the pharmacokinetics of the drug and biopharmaceutics of the drug product characterized?

Pharmacokinetics of LNG are provided by the sponsor from a relative bioavailability study comparing the to-be-marketed formulation to a suspension. Pharmacokinetics and clinical pharmacology of LNG is also well cited in the literature.

Absorption: LNG undergoes rapid absorption after oral administration, with the Tmax of 1-2 hours. An average Tmax of about 1.6 hours was reported in Study WCC-PK-001 with the commercial formulation. Influence of coadministration with meals has not been characterized.

Distribution: LNG is extensively bound (50% to albumin and 47.5% to sex hormone binding globulin, SHBG) with low affinity and high capacity to albumin and high affinity and low capacity to SHBG. Only about 2.5% is unbound. Administration of LNG decreases SHBG levels with the maximum effect approaching after about 1 week. A single dose of 0.75mg LNG has been reported to result in about 25% reduction in SHBG. The study published by He, et.al. reported a reduction in SHBG by about 8% after a single 0.75mg dose of LNG at 24 hours after a single dose.

Metabolism: LNG is reported to have minimal first pass elimination and is a low extraction drug (bioavailability of about 100%). Enterohepatic recirculation has not been reported. Although no mass balance studies were conducted in this NDA, based on published literature, four tetrahydrometabolites were identified, with 3α,5β- and 3α,5α-isomers as the major compounds. Monohydroxylated metabolites (2α and 16β) were also detected. Together, these metabolites are present in $1/10^{th}$ the concentration as LNG. Small amounts were detected as sulfates and glucuronide conjugates. Isozymes responsible for the metabolic pathways have not been characterized.

Excretion: A distribution phase with a t1/2 of about 1-3 hours followed with a longer elimination phase with a t1/2 ranging from 3-29 hours have been reported in the literature with oral LNG formulations, which may be due to sampling duration across studies. The t1/2 for LNG was reported as about 24 hours after LNG administration. LNG is a low extraction drug. An apparent clearance of about 7.7 L/hr was reported for the commercial formulation.

Pharmacokinetics in Special Populations:

Geriatric and Pediatric Populations:
This product is not intended for use in geriatric or pediatric (premenarchal) populations, and pharmacokinetic data are unavailable for these populations.

Race:
No formal studies have evaluated the effect of race. Clinical trials demonstrated a higher pregnancy rate in the Chinese population with both PLAN B™. The reason for this apparent decrease in the efficacy of ECs in Chinese women is unknown. It should be noted that the study WCC-PK-001 in 16 females included 1 Asian Pacific subject who showed the lowest AUC amongst all subjects tested. It is not known whether this can be generalized for all Asian population and whether this can be the potential cause of higher pregnancy rate in this ethnic group

Hepatic Insufficiency, and Renal Insufficiency:
No formal studies have evaluated the effect of hepatic and renal insufficiency on the disposition of ECs. However, steroid hormones may be poorly metabolized in women with impaired liver function. Since PLAN B is intended for a relatively young and healthy population, hepatic or renal insufficiency may not be of a major concern in clinical practice.

Is it necessary to individualize dose based on demographic characteristics ?

Although the clinical trials included Asians and demonstrated higher pregnancy rates in this population, the same dose (2 of 0.75mg tablets taken 12 hours apart) has been recommended for clinical use in all subjects. Since high variability is associated with this drug, it is possible that lower efficacy is not caused by lower levels of LNG. However, without an adequate dose finding study and an established pharmacokinetic and pharmacodynamic relationship, this cannot be definitively ruled out. Unless there is a clinical reason for higher pregnancy rates in the Asian subgroup, the possibility of higher doses in this population could be explored. An attempt should be made to definitively rule out lower plasma concentrations as a possible cause of higher pregnancy rates. Note that the study conducted by He, et al, 1990, compared a Chinese pill to Postinor (Hungarian tablet similar to PLAN B) and showed differences in exposure (about 25% for AUC and 100% for Cmax), however, the pregnancy rates were similar for both products.

Is there a potential for drug-drug interactions ?

Formal studies to address drug-interaction potential for LNG were not performed. Literature reports (Steroid Contraceptives and Women's Response, Back and Orme, 103) suggest that coadministration with phenytoin and carbamazepine may induce LNG metabolism, resulting in lower LNG exposure. Although the impact on efficacy of PLAN B is not known, potential for interaction exists and this has been addressed in the label. The sponsor is encouraged to explore the metabolic enzyme pathways and the specific drug interaction potential for LNG in PLAN B.

Are the in-vitro dissolution specifications acceptable?

Sponsor proposed dissolution method:

Apparatus:	Paddle (USP Method II)
Rotation Speed:	75 rpm
Dissolution Medium:	0.1 N HCl with 1g/liter sodium lauryl sulfate (SLS), 1 liter
Sampling Times:	5, 15, 30, 45, 60, 75, 90 min
Proposed specification:	**Q % at minutes**

The sponsor has provided the justification for the use of this method (Attachment). Based on the dissolution results, the sponsor's proposed specification is not acceptable. The FDA recommended specification, using the above method, is **Q % at . ninutes.**

In summary, the sponsor investigated various dissolution media, rpms, and volumes prior to finalizing with the above procedure, as follows :
Rpm: 75 rpm (12 tablets from 3 batches) comparison to 50 rpm (12 tablets from 1 batch)
Volume: 900 ml vs 1000 ml 0.1 N HCl containing 1g/L SLS
Surfactant Concentration: 0.1 N HCl with SLS (0, 0.0001g/L, 0.001g/L, 0.01g/L, 0.1g/L)
Acid vs water: acid and water with SLS (0, 0.0001g/L, 0.001g/L, 0.01g/L, 0.1g/L, 1g/L)
USP procedure for LNG/ethinyl estradiol: paddle 75 rpm, water containing 5mg/L polysorbate 80; 500 ml versus sponsor proposed method

The dissolution results show that:
The paddle speed of 50 rpm results in slow dissolution with only about % dissolved at minutes.
Dissolution was slow without the surfactant in the medium and improved with increasing concentrations of surfactant. With the final in-vitro method chosen by the sponsor, levonorgestrel dissolution was about % in minutes.

Having established a dissolution method for in-vitro quality assurance, the sponsor compared the clinical trial batch and the to-be-marketed formulation (formulation differences were discussed at the pre-NDA meetings and considered minor). The dissolution profiles from the clinical and to-be-marketed lots are similar (f2>50).

Is the label appropriate ?

The original label submitted with the NDA has been modified to include the suggestions regarding clarification of the clinical pharmacology and biopharmaceutics section.

Is the NDA acceptable from pharmacokinetic perspective ?

Absorption, distribution, metabolism and elimination for LNG have been characterized in the literature. NDA 21-045 has conducted a relative bioavailability study characterizing the commercial PLAN B formulation. In-vitro dissolution method and specifications have been proposed by the sponsor. The NDA is acceptable from the OCPB/DPEII perspective provided the dissolution specification is tightened by the sponsor (Q % in minutes).

The pharmacokinetics/clinical pharmacology studies provided in this application include:

1. Study WCC-PK-001: Relative bioavailability study of the commercial tablet formulation to a suspension of micronized LNG.

2. Three published studies, either as single (comparison to other products) or multiple dose (7 days) using Postinor (the earlier formulation by

3. Additional literature articles addressing pharmacokinetics of LNG.

4. In-vitro dissolution methodology and testing.

Analytical methodology for the WCC-PK-001 study utilized a validated assay

STUDY SUMMARIES:

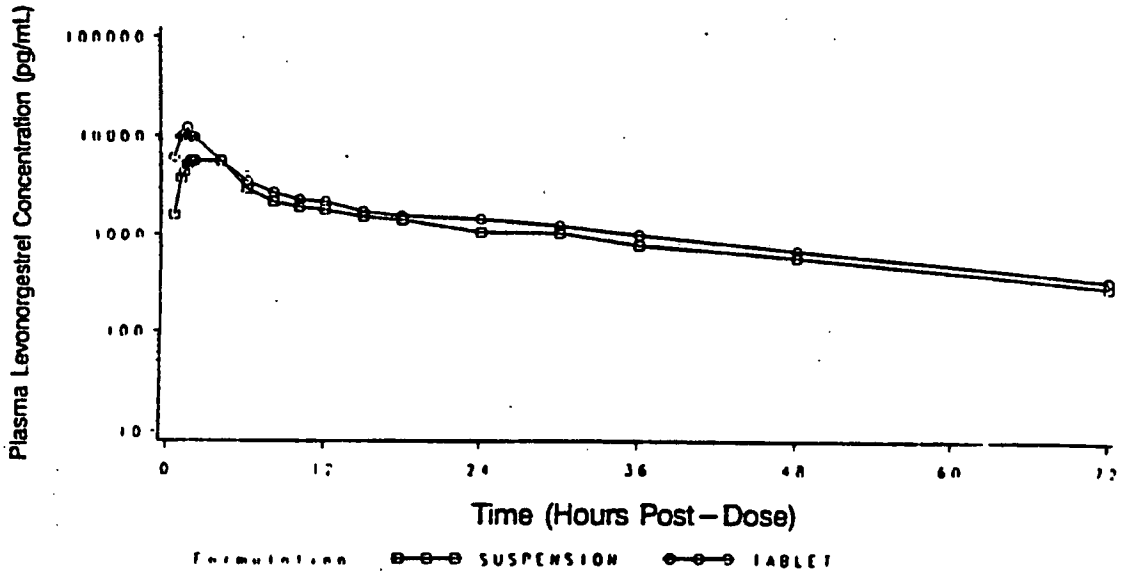
WCC-PK-001: A two-period cross-over study of relative bioavailability of LNG commercial 0.75mg tablet to a suspension of micronized LNG drug substance, administered to fasting female volunteers (details attached).

Sixteen healthy female volunteers (18-45 years) were administered the suspension and tablet formulations separated by a washout of 1 week. Plasma samples were collected 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 after dosing and pharmacokinetics of LNG were characterized for the tablet, relative to the suspension. A summary of the results are attached.

Mean Pharmacokinetic Parameters and Ratios of 0.75 mg Levonorgestrel Table: Versus 0.75 mg Levonorgestrel Suspension Micronized

	Mean AUC_{0-t} (pg*hr/mL)	Mean AUC_{0-inf} (pg*hr/mL)	Mean Cmax (pg/mL)	Ratio AUC_{0-t}	Ratio AUC_{0-inf}	Ratio Cmax
Table:	111775	123114	14111	1.40	1.37	2.15
Suspension	84260	95485	7519			

Mean Plasma Levonorgestrel Concentrations
(Semi–Log Plot)



In general, WCC-PK-001 showed that LNG from PLAN B undergoes a rapid absorption with a short distribution phase, followed by an elimination t1/2 of about 24 hours. The AUCs ranged from 62511 - 222142 pg*hours/ml (3 fold range) and Cmax values ranged from 6657-38990 pg/ml (5-6 fold range) between subjects. High inter- and intra-subject variability has also been reported for LNG in the literature. The only Asian Pacific female subject in WCC-PK-001 showed AUC and Cmax values of 62511 pg*hours/ml and 9448 pg/ml respectively. The relative bioavailability of the tablet compared to the suspension was 137% and the Cmax ratios were 2.15. The lower bioavailability of suspension was unexpected. These differences were significant and explained by the sponsor to be due to environmental static charge potentially causing the micronized LNG to aggregate.

He, et.at., Contraception 1990;41,557: A randomized single dose cross-over relative bioavailability study of two marketed formulations of 0.75mg LNG (Hungarian and Chinese formulations) in 10 normal healthy females. The Hungarian formulation is similar to the U.S. to-be-marketed formulation. Both formulations were tested in a published clinical trial and shown to have a failure rate of about 1.1%.

Blood samples were obtained at pre-dose and at 1, 2, 4, 8, 12 and 24 hours after taking the tablets. The plasma samples were analyzed for LNG by a published radioimmunoassay.

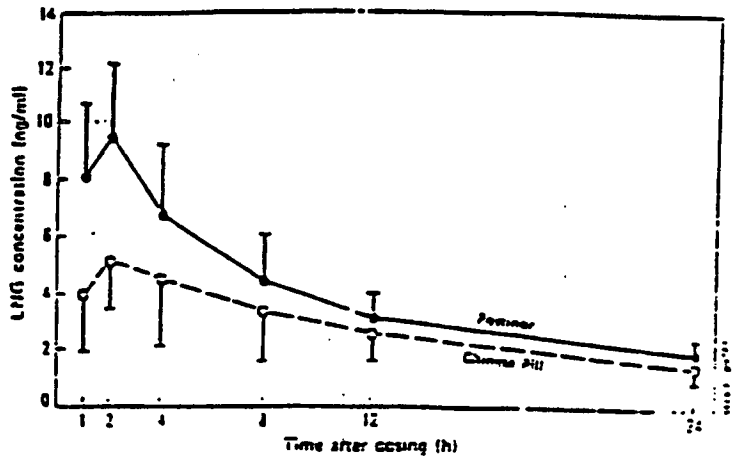
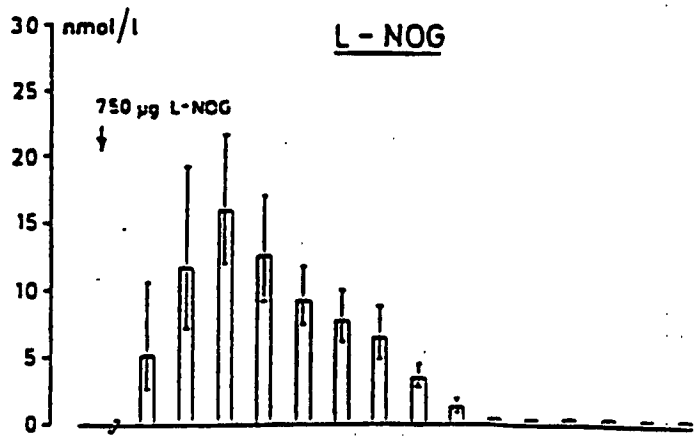


Fig. 1. Serum levonorgestrel concentrations (means and SD) after oral administration of two different formulations each containing 0.75 mg levonorgestrel

Serum concentrations we higher with the Hungarian tablet (POSTINOR). AUCs reported were about 25% higher and Cmax values were almost double and significantly different. A 2-3 fold inter-subject variability was reported for both tablets. SHBG concentrations were similar for both groups at pre-treatment stage (about 50nmol/L) and about 8% reduction was reported for SHBG at 24 hours after single dose. The differences in bioavailability may be attributed to the particle size distribution of micronized LNG (73% vs. 10% below 23μm). The latter evidence supports the findings from the relative bioavailability study with the suspension (WCC-PK-001) where particle size of the suspension were expected to have aggregated and effectively larger than the commercial tablet. NOTE that the AUC for POSTINOR from this study averaged around 124000 (range 66800-176600) pg.hours/ml which is in the range of values observed for the commercial product. This article reports that these products were not clinically different.

Landgren, et.at., Contraception 1989;39,275: A single 0.75mg dose study in 10 healthy females. Plasma samples drawn immediately before and at 0.5, 1, 2, 4, 8, 12, 48, 72, 120, 144, 168 and 192 hours after LNG intake. A separate pharmacodynamic study included 72 females from Stockholm, Shanghai and Bombay, who randomly took 4 tablets of 0.75mg LNG on different days of the cycle to study the effect of LNG administered during follicular, periovulatory and luteal phases. Blood samples were drawn 3 times per week and quantitated for estradiol and progesterone. An average Cmax of about 17nmol/l (about 5312pg/ml).



Suppression of ovarian function was seen when LNG was administered in the late follicular phase and around the time of ovulation. When administered in the follicular phase, the proliferative activity of LNG, (as measured by a decrease in number and diameter of glands) was suppressed. When administered in the secretory phase, no change in the endometrium were observed. Based on this study, the postcoital action of LNG is probably due to a combined effect pituitary-ovarian function, endometrium and cervical secretions.

Shi, et.at., Contraception 1988;37,359: This is a multiple dose study of 0.75mg LNG once daily for 7 days during the periovulatory phase of the menstrual cycle. Plasma samples were collected on day 1 at pre-dose and 1, 2, 4, 8 and 12 hours after administration of LNG. On days 2-6, blood samples were taken prior to dosing. On day 7, blood samples were again collected at pre-dose and at 1, 2, 4, 8, 12 and 24 hours after administration of LNG and then on days 11 and 13. Plasma concentrations of LH, FSH, prolactin, estradiol, progesterone and LNG were determined using a radioimmunoassay.

No accumulation was observed with multiple dosing of LNG once daily. Steady state seemed to have reached by 48 hours. It was noted that while the midcycle elevations in LH were suppressed, mid-cycle estradiol peaks and luteal phase increases in progesterone were observed. The low failure rate obtained in clinical trials may suggest multiple pathways of action (reproductive tract and the pituitary ovarian suppression).

Table 6.6
Comparison of Clinical Trials and Commercial Batch
Levonorgestrel 0.75 mg Tablets

Components	Quantity per Tablet (mg)	
	1995 Clinical Batch (WHO # 20786-0195-001) "Pre-1996 Formulation"	Proposed Commercial Formulation
Levonorgestrel	mg*	mg
Colloidal silicon dioxide	mg	mg
Potato starch	mg	mg
Magnesium stearate	mg	mg
Gelatin	mg	mg
Talc	mg	mg
Corn starch	mg	mg
Lactose	mg	mg
Fill Weight:	mg	mg

* 5% overage added

E. ANALYTICAL METHODS

WCC-PK-001

2 SYNOPSIS

Name of Sponsor/Company: Women's Capital Corporation		
Name of Finished Product: Not available		
Name of Active Ingredient: 0.75 mg Levonorgestrel		
Title of Study: Protocol Number:	A two period, crossover study of the relative bioavailability of levonorgestrel 0.75 mg tablets administered orally to fasting female volunteers. WCC-PK 001	
Investigator:		
Study Site:		
Authors:		
Study Period:	Date first patient enrolled: July 27, 1998 Date last patient completed: August 6, 1998	
Primary Objectives:	• To study the bioavailability of levonorgestrel 0.75 mg tablets relative to a suspension of micronized levonorgestrel drug substance when administered to fasting female volunteers.	
Secondary Objective:	• To characterize levonorgestrel pharmacokinetics in this sample.	
Methodology	Randomized, two-way crossover, single-center study of relative bioavailability	
Number of Subjects (planned and analyzed):		Total
	Planned	16
	Enrolled	16
	Discontinued	0
	Completed	16
• Diagnosis and Main Criteria for Inclusion:	Sixteen, healthy, adult female volunteers between the ages of 18 and 45 years.	
Test product, dose and mode of administration, batch number:	0.75 mg levonorgestrel table: Batch No. T7B415A	
Duration of treatment:	At least 11 days	
Reference product, dose and mode of administration, batch number:	Suspension of 0.75 mg levonorgestrel Batch No. JS2027K	

Name of Sponsor/Company: Women's Capital Corporation

Name of Finished Product: Not available

Name of Active Ingredient: 0.75 mg Levonorgestrel

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

The pharmacokinetic parameters AUC_{0-T}, AUC_{0-inf}, and Cmax were greater (40%, 37% and 115%, respectively) from the tablet formulation than the suspension formulation. In addition, the tablet formulation demonstrated a faster time to maximum concentration (mean 1.6 hrs vs. 2.8 hrs). The two one-sided test procedure on the pharmacokinetic parameters AUC_{0-T}, AUC_{0-inf}, and Cmax showed that the 0.75 mg levonorgestrel tablet and the 0.75 mg levonorgestrel micronized suspension were not bioequivelent in the extent (AUC_{0-T}, AUC_{0-inf}) or rate of absorption (Cmax).

SAFETY RESULTS:

Both formulations of levonorgestrel were safe and well tolerated by the 16 healthy women enrolled in this study.

CONCLUSION:

From this study it was concluded that the levonorgestrel 0.75 mg tablet was not bioequivalent to the 0.75 mg levonorgestrel micronized suspension with respect to plasma pharmacokinetic parameters. Both formulations of levonorgestrel were safe and that the study drug was well tolerated.

Date of the Report: 20/JAN/99

Project Number :981184
LEVONORGESTREL in Human Plasma
Pharmacokinetic Parameters by Formulation
Formulation: TABLET (A)

Race	Subject ID	Period	AUC 0-t (pg·h/mL)	AUCinf (pg·h/mL)	Cmax (pg/mL)	tmax (h)	kel (1/h)	Half-life (h)	MRT (mL/h)	CL/F (mL/h)	Vdß (mL)
W	1	2									
W	2	2									
A	3	1									
A	4	1									
W	5	2									
B	6	1									
W	7	1									
W	8	2									
B	9	2									
W	10	1									
W	11	1									
B	12	2									
W	13	2									
W	14	1									
B	15	1									
W	16	2									
Arithmetic Mean			111774.458	123113.820	14111.43	1.634	0.0298	24.439	27.752	7056.691	259967.639
± SD			49162.3600	50129.3586	7677.235	0.7404	0.00723	5.3400	5.1727	2690.4995	129535.7563
CV%			44.0	40.7	54.4	45.3	24.3	21.9	18.6	38.1	49.8
n			16	16	16	16	16	16	16	16	16

W = (White) Caucasian
A = Asian/Pacific
B = African

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Table 11.5.2.1-3: Mean Plasma Concentrations of 0.75 mg Levonorgestrel Suspension Micronized (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	7.7	1587.7	3736.0	4299.0	5080.1	5491.9	5613.9	5574.2	2904.7	2137.4
SD	21.1	1212.3	2528.7	2657.8	3098.4	2788.2	2788.3	3867.8	1693.8	1176.7
		10	12	15	18	24	30	36	48	72
Mean		1881.2	1759.5	1487.8	1373.25	1021.0	995.8	741.4	549.2	280.0
SD		906.1	844.9	788.3	616.4	437.3	455.1	358.7	231.3	102.3

Source Data: Appendix 14.2-1, Table 4.

Table 11.5.2.1-4: Mean Pharmacokinetic Results of 0.75 mg Levonorgestrel Suspension Micronized

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	84260.4	95485.2	7519.4	2.8	27.3	31.6	9.6	378.9
SD	35409.3	38196.5	4144.9	1.1	6.3	6.0	5.1	224.0

Source Data: Appendix 14.2-1, Table 6

11.5.2.2 Relative Bioavailability

The pharmacokinetic parameters AUC_{0-t}, AUC_{0-inf}, and Cmax were greater (40%, 37% and 115%, respectively) from the tablet formulation than the suspension formulation, Table 11.5.2.2-1. In addition, the tablet formulation demonstrated a faster time to maximum concentration (mean 1.6 hrs vs. 2.8 hrs). The two one-sided test procedure on the pharmacokinetic parameters AUC_{0-t}, AUC_{0-inf}, and Cmax showed that the 0.75 mg levonorgestrel tablet and the 0.75 mg levonorgestrel micronized suspension were not bioequivelent in the extent (AUC_{0-t}, AUC_{0-inf}) or rate of absorption (Cmax), Table 11.5.2.2-2.

Table 11.5.2.2-1: Mean Pharmacokinetic Parameters and Ratios of 0.75 mg Levonorgestrel Tablet Versus 0.75 mg Levonorgestrel Suspension Micronized

	Mean AUC_{0-t} (pg*hr/mL)	Mean AUC_{0-inf} (pg*hr/mL)	Mean Cmax (pg/mL)	Ratio AUC_{0-t}	Ratio AUC_{0-inf}	Ratio Cmax
Tablet	111775	123114	14111	1.40	1.37	2.15
Suspension	84260	95485	7519			

Source Data: Appendix 14.2-1, Tables 7, 8 and 9

GENERAL OVERVIEW OF STUDIES

WCC-PK-001

He, et.al., Contraception, 1990: 41, 557

Landgren, et.al., Contraception, 1989: 39, 275

Shi, et.at., Contraception 1988;37,359

Table 6.1
Overview of Clinical Pharmacokinetic Studies Conducted with Levonorgestrel 0.75 mg

Study No. (Date*)	N [M/F]	Ethnicity (Country)	Age (yrs) Mean ± SD [range]	Weight (kg) Mean ± SD [range]	Design	Dose
WCC-Sponsored Study of Proposed Commercial Formulation						
WCC-PK 001 (1998)	16 [0/16]	9 White 6 Black 1 Asian/Pacific Islander (United States)	28 ± 9 [19-44]	65.3 ± 9.9 [50.8-79.2]	Single dose, two-period, crossover bioavailability study	0.75 mg
Other Studies Performed with Gedeon Richter Formulations						
He *et al.* (1990)	10 [0/10]	– (China)	27.4 ± 3.7 [–]	53.8 ± 5.9 [–]	Randomized, double blind, multicenter, crossover study	0.75 mg
Landgren *et al.* (1989)	10 [0/10]	– (Sweden)	32.4 [30-39]	–	Single dose study	0.75 mg
Shi *et al.* (1988)	6 [0/6]	– (China)	– [27-35]	– [48-60]	Multiple dose study for 7 days	0.75 mg
TOTAL	42 [0/42]	–	– [19-44]	– [48-79.2]		

* Date of study conduct or in the case of publications, date of publication.

Table 6.2
Tabular Summary of Pharmacokinetic Studies, Formulations Used, and Results

Study Number	Route of Admin.	Study Design Dosage Form	Dose	Batch No. Manufacturer Date of Manufacture	No. of Subjects	Submission Date	Applicant Conclusion
WCC-Sponsored Study of Proposed Commercial Formulation							
WCC-PK 001 1998	Oral	Two-period, crossover study of tablets and a micronized suspension	0.75 mg	Tablet: T7B415A Date of Manufacture: 11/97 Drug Suspension: J82027K Date of Manufacture: 3/98	16	Final protocol submitted to IND 010 (7/21/98)	The tablet and suspension weren't bioequivalent in extent or rate of absorption. AUC$_{0-\infty}$ and C$_{max}$ were greater (37% and 115%, respectively) from the tablet formulation than the suspension formulation. In addition, the tablet formulation demonstrated a faster time to maximum concentration (mean 1.6 hours vs. 2.8 hours). Serum levels declined with a mean terminal half-life of 24.4 ± 5.3 hours following administration as a tablet and 27.3 ± 6.3 hours following administration as a suspension.
Other Studies Performed with Gedeon Richter Formulation							
He *et al.*, 1990	Oral	Randomized, double-blind, multicenter, crossover study of two tablet formulations	0.75 mg 0.75 mg	Batch No.: N/A (Postinor) Date of Manufacture: N/A Batch No.: N/A Date of Manufacture: N/A	10	Not applicable	In both groups there was a 2- to 4-fold between-subject variation in levonorgestrel concentrations at all times between 2 and 24 hours. Single dose mean peak serum level for Postinor was 11.2 ng/mL; which occurred on average 1.9 hours post dose. There was a progressive decrease in levels of SHBG over the study period.

Table 6.2 continued
Tabular Summary of Pharmacokinetic Studies, Formulations Used, and Results

Study Number	Route of Admin.	Study Design Dosage Form	Dose	Batch No. Manufacturer Date of Manufacture	No. of Subjects	Submission Date	Applicant Conclusion
Landgren *et al.*, 1989	Oral	Single dose study of a tablet	0.75 mg	Batch No.: N/A Date of Manufacture: N/A	10	Not applicable	Peak levonorgestrel levels were achieved by 2 hours post-dose. Elimination half-life was 14.5 hours.
Shi *et al.*, 1988	Oral	Multiple dose study of one tablet given daily for 7 days	0.75 mg	Batch No.: N/A Date of Manufacture: N/A	6	Not applicable	There was a 2- to 3-fold variation in peak concentration in different women. First dose peak concentration ranged from [illegible] ng/mL, occuring 2 to 4 hours post-dose. Mean half-life of elimination was 8.9 hours, ranging from [illegible] hours.

N/A= Not available

Table 6.3
Summary of Pharmacokinetic Parameter Values for Studies with Manufactured Levonorgestrel

Study	N	Dose	Mean (± S.D.)						
			C_{max} (ng/mL)	T_{max} (h)	T_a (h)	T_β (h)	V_d (L)	CL (L/h)	AUC_{∞} (ng/mL/h)
WCC-Sponsored Study of Proposed Commercial Formulation									
WCC-PK 001	16	0.75 mg	14.1 ± 7.7	1.6 ± 0.7	–	24.4 ± 5.3	260.0	7.7 ± 2.7	123.1 ± 50.1
Other Studies Performed with Formulation									
He *et al.* 1990	10	0.75 mg	11.2 ± 3.4	1.9 ± 0.6	1.3 ± 0.6	13.3 ± 3.7	115 ± 41	6.1 ± 1.9	124 ± 43
Landgren *et al.* 1989	10	0.75 mg	16.0	–	–	14.5	–	–	–
Shi *et al.* 1988	6	0.75 mg	9.0 ± 2.2	2-4	–	8.9 ± 1.9	88.6 ± 25.6	7.2 ± 2.7	116 ± 41

3. Age Effects

Due to the limited age range of women participating in these studies (19 to 44 years), and given that the target population for levonorgestrel emergency contraception is comparable, age effects have not been evaluated.

4. Ethnicity Effects

Pharmacokinetic parameters have been summarized separately be ethnicity. Ethnicity was not stated in the three published studies conducted using the levonorgestrel tablet. Two studies were conducted in China and, presumably, all 16 subjects were Chinese. Similarly, the ten subjects participating in Sweden are all assumed to be Caucasian. There is a suggestion of lower concentrations in Asian subjects. These observations, summarized below in Table 6.4, should be interpreted with caution, however, as in the U.S.-based study, there was only one Asian subject, and the assay methodology in the other studies differed.

Table 6.4
Summary of Levonorgestrel 0.75 mg Single Dose Tablet Pharmacokinetic Parameter Values by Ethnicity

Parameters	WCC-PK 001			Landgren *et al.*, 1989 — (Sweden) (N=10)	He *et al.*, 1990 — (China) (N= 10)	Shi *et al.*, 1988 — (China) (N= 6)
	Caucasian (U.S.) (N=9)	Black (U.S.) (N=6)	Asian/ Pacific Islander (U.S.) (N=1)			
C_{max} (ng/mL)	15.9	12.2	9.4	16.0	11.2 ± 3.4	9.0 ± 2.2
T_{max} (h)	1.8	1.4	1.3	—	1.9 ± 0.6	2-4
$AUC_{0-\infty}$ (ng/mL/h)	131.5	120.7	62.5	—	124 ± 43	116 ± 41
Half life (h)	24.6	24.5	22.9	14.5	13.3 ± 3.7	8.9 ± 1.9
C_L (L/hr)	6.4	7.2	12.0	—	6.1 ± 1.9	7.2 ± 2.7

5. Special Populations

No formal pharmacokinetic studies have been conducted in patients with renal or hepatic impairment. Since the product is administered as a single dose (two separate administrations) there is no concern about the potential accumulation that might occur with chronic dosing in patients with hepatic or renal impairment.

D. LIST OF FORMULATIONS

has been commercially manufacturing levonorgestrel 0.75 mg tablets since 1980. They have supplied drug product for numerous clinical studies of safety and efficacy conducted by UNDF/UNFPA/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (WHO/HRP). They have also supplied the Women's Capital Corporation (WCC)-sponsored study (WCC-PK 001) and studies sponsored by WHO/HRP and published by Landgren *et al.* (1989), He *et al.* (1990), and Shi *et al.* (1988). The batch used in the WCC-PK 001 study represents the proposed commercial formulation, and also does not differ substantially from the formulation used in the clinical trials.

An overall summary of the drug product batches used in pharmacokinetic studies of levonorgestrel 0.75 mg tablet is provided in Table 6.5 and a summary of the composition of each formulation is presented in Table 6.6. Since the drug product for the WHO/HRP pivotal clinical study (WHO/HRP 1998 - Study 92908) was manufactured (Batch # 20786-0195-001), two minor changes have been made to the

Table 6.5
Drug Formulation Summary

Study Number	Drug Product Batch Number	Dosage Form and Strength	Drug Product (Substance) Batch Size	Formulation Code*	Drug Substance Batch Number
WCC-Sponsored Study of Proposed Commercial Formulation					
WCC-PK 001 1998	T7B415A N/A	0.75 mg tablet 0.75 mg suspension	tablets (30- 37 kg)	Proposed Commercial Formulation N/A	J6C0700 J82027K
Other Studies Performed with Formulation					
He *et al.*, 1990	N/A	0.75 mg tablet	N/A	N/A	N/A
Landgren *et al.*, 1989	N/A	0.75 mg tablet	N/A	N/A	N/A
Shi *et al.*, 1988	N/A	0.75 mg tablet	N/A	N/A	N/A
Efficacy Studies of Levonorgestrel as Emergency Contraception					
WHO/HRP 1998 - Study 92908	20786-0195-001	0.75 mg tablet	N/A	1995 Clinical Batch	N/A
WHO 81107 (Ho & Kwan)	N/A	0.75 mg tablet	N/A	N/A	N/A

N/A= Not available
* Refer to Table 6.6 for composition of formulations

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F. *IN VITRO* DISSOLUTION

1. Introduction

tests drug product as part of the release procedure. Based on dissolution profiles, the dissolution specification described below has been proposed. Final release testing was also performed by for the lot used in the recent Women's Capital Corporation-sponsored WCC-PK 001 study. Experiments using various media, paddle speeds, and sampling time points are underway at .

2. Proposed *In Vitro* Dissolution Specification

The proposed dissolution testing method and specification for levonorgestrel 0.75 mg tablets are summarized below. A copy of dissolution testing method for levonorgestrel drug product is provided in Appendix 6.2. A copy of the dissolution profile is also included. Six tablets per lot were analyzed using and all met the proposed specification. Please refer to Section F.4 for more detailed information on these lots.

Apparatus:	Paddle stirring element (USP Method II)
Medium:	1000 mL of 0.1 N hydrochloric acid solution containing 1 g of sodium laurylsulphate
Speed:	75 rpm
Temperature:	Room temperature

Sampling Times: minutes

Assay Method:

Proposed Specification: Q % at minutes

3. Summary of Supporting Studies

Experiments using various media, paddle speeds, and sampling time points are underway at Dissolution profiling will be performed on 12 tablets from each of three batches of drug product. Results for this study are anticipated in January 1999. Please refer to Appendix 6.2 for a copy of the dissolution protocol.

4. Testing Results for Key Batches

tests drug product as part of the release specifications. Four lots had been analyzed for dissolution profiles. Lot # 20786-0195-001 (Table 6.8) was the batch used for the WHO/HRP 1998 - Study 92908, this batch is known as the "1995 Clinical Batch". Tables 6.9 to 6.11 represent three lots that were used for packaging tests and stability testing on drug product packaged at

a. 1995 Clinical Batch (WHO/HRP 1998 - Study 92908)

Table 6.8
Lot Number 20786-0195-001: Percent Dissolution

Tablet #	10 minute	20 minutes	30 minutes	45 minutes	60 minutes
1					
2					
3					
4					
5					
6					
Mean	69.3	80.9	84.9	88.6	90.9
RSD (%)	4.3	3.1	2.0	1.2	2.8

b. Batches Used for Packaging Tests and Stability

Table 6.9
Lot Number T73354: Percent Dissolution

Tablet #	10 minute	20 minutes	30 minutes	45 minutes	60 minutes
1					
2					
3					
4					
5					
6					
Mean	66.1	79.0	83.5	88.2	88.5
RSD (%)	4.1	3.2	1.8	1.6	1.3

Table 6.10
Lot Number T73355: Percent Dissolution

Tablet #	10 minute	20 minutes	30 minutes	45 minutes	60 minutes
1					
2					
3					
4					
5					
6					
Mean	69.7	79.3	83.5	86.1	88.1
RSD (%)	9.3	3.8	2.0	2.8	2.5

Table 6.11
Lot Number T73358: Percent Dissolution

Tablet #	10 minute	20 minutes	30 minutes	45 minutes	60 minutes
1					
2					
3					
4					
5					
6					
Mean	64.1	77.6	81.7	85.4	88.3
RSD (%)	3.4	6.0	2.9	2.8	3.3