

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21045

ADMINISTRATIVE DOCUMENTS

Group Leader Memorandum

JUN 21 1999

NDA: 21-045

Drug: Levonorgestrol Tablets (0.75 mg)
Plan B™

Indications: Emergency Contraception

Dose/Regimen: 1 tablet (0.75 mg) taken orally within 72 hours of unprotected intercourse with a repeat dose 12 hours later

Applicant: Women's Capital Corporation
Drug Manufacturer: Gedeon Richter, Hungary

Original Submission: 1/29/99
Review Completed: 6/7/99
Date of Memorandum: 6/21/99

I. Background

Emergency contraception is the use of a drug or device to prevent pregnancy within a few hours to a few days of unprotected sexual intercourse.

The first drug to be FDA approved for emergency contraception is Preven®, approved on September 2, 1998. Preven is an ECP regimen comprised of 2 tablets of ethinyl estradiol (0.1 mg) plus levonorgestrol (0.5 mg) taken within 72 hours of unprotected intercourse with repeat dosing 12 hours later. It is an example of the Yuzpe regimen, which is named after Dr. Albert Yuzpe, a clinician who evaluated a number of combination estrogen/progesterone products as emergency contraceptive regimens in the 1970-1990 timeframe. The most successful regimen was the combination of 0.1 mg ethinyl estradiol and 1 mg norgestrol taken 12 hours apart, within 72 hours of unprotected intercourse. This became known as the "Yuzpe regimen." In 1997, the FDA reported in the Federal Register that certain combined oral contraceptive regimens containing ethinyl estradiol and levonorgestrol (or norgestrol) were safe and effective for use as emergency contraceptives. Most importantly, this notification stated that controlled clinical trials were not necessary for the drug combinations listed if a sponsor should decide to pursue FDA approval. Therefore, the Preven NDA did not include clinical trial data, but was based on this Federal Register notice. Since the approval of Preven, no other products have been approved as emergency contraceptives.

The FDA's acknowledgement of combined oral contraceptive regimens as safe and effective oral contraceptive regimens in the 1997 Federal Register Notice did not include levonorgestrol-alone products. Notably, levonorgestrol 0.75 mg tablets are marketed in 34 countries outside the U.S. as emergency and/or routine post-coital contraceptives.

Memorandum

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Date: JUN 27 1999
From: David Hoberman, Ph.D., HFD-715
Subject: Levonorgesterol for Emergency Contraception
To: File (NDA# 21-045)

The WHO/HRP 1998 - Study 92908 was a randomized controlled trial comparing levonorgesterol (two doses of .75 mg taken 12 hours apart) to the Yuzpe regimen (high-dose combined oral contraceptive) as emergency contraception within 72 hours after unprotected intercourse. After consulting with Dr. Davis and other staff of HFD-580, it was decided that the primary clinical endpoint was the incidence of pregnancy in the two groups (N=976: levonorgesterol and N=979: Yuzpe regimen). The sponsor reported a total of 42 pregnancies: 11 in the levonorgesterol group and 31 in the Yuzpe group. After reviewing the data, Dr. Davis concluded that there were actually 37 incident pregnancies: 10 in the levonorgesterol group {1.0%, 95% CI (0.5% to 1.9%)} and 27 in the Yuzpe group {2.75%, 95% CI (1.8% to 4.0%)} The p-values comparing the two treatment groups are less than .01 in both the sponsor's and the FDA's analyses.

Reviewer's Comment

This trial suffers from a possible critical design flaw. There was no "objective" determination of pregnancy such as a urine test (the patient came into a clinic when she suspected she might be pregnant). Consequently, there may be 'detection bias' in the evaluation of pregnancy on the two arms; i.e., if there were reasons that women's pregnancies had a greater probability of being detected in one group or the other, the estimates of differential pregnancy could be biased.

For example, if just 5 pregnancies were missed (due to spontaneous abortion or whatnot) on the levonorgesterol arm and none were missed on the Yuzpe arm, the p-value comparing the groups would be .06, not statistically significant. This sensitivity analysis reveals the non-robustness of the data which lends support to the position of not granting a superiority claim to levonorgesterol.

The Role of Chinese Women

It appears that (pooling the two groups) there was less efficacy in Asian (including Mongolian) women. If all other ethnic backgrounds are pooled, and if Asians had the same rate as the others, approximately 9 pregnancies would be expected in the Asian group; however, there were actually 19. However, no firm conclusion can be drawn from this small number of events. Nevertheless, it is of interest to compare the two treatment groups leaving out the 500 Chinese women only, since there were no pregnancies among the 150 Mongolian women. The resulting pregnancy incidence was 5/726 (0.7%) in the levonorgesterol group and 13/729 (1.8%) in the Yuzpe group. The p-value for this comparison of proportions is .052.

As regards safety, the sponsor found that the levonorgesterol group had statistically significantly less nausea, vomiting, fatigue and dizziness than the Yuzpe regimen ($p < .01$ for each of the 4 symptoms).

One other observation of interest to Dr. Davis is noted here:

There was a tendency for the incidence of pregnancy to increase the longer the women waited to take medication (pooling the two groups). In the intervals 0-24 hours, 25-48 hours, and >48 hours, the percentages were 1.2% (11/909), 2.1% (15/708), 33% (11/36), respectively. The p-value comparing the 0-24 interval to the >48 hour interval was .025 (two-sided).

/s/

David Hoberman, Ph.D.

Concur: Dr. Kammerman *PK 6/18/99*

Dr. Nevius *SN 6/27/99*

cc:

Arch NDA# 20-045

HFD-580

HFD-580/DDavis, MMann

HFD-715/DHoberman, DOB2, Chron

EXCLUSIVITY SUMMARY FOR NDA # 21-045

Trade Name PLAN B™ Generic Name levonorgestrel 0.75 mg Tablets

Applicant Name Women's Capital Corporation HFD # 580

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?
YES / NO /

b) Is it an effectiveness supplement?
YES / NO /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / NO /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / X / NO / ___ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES / ___ / NO / X /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / ___ / NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 17-031 Ovrette

NDA# 20-544 Norplant II

NDA# 20-683 Aless

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / /

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

WHO/HRP 1998 - Study 92908

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____ YES / X / ! NO / ___ / Explain: _____
! _____
! _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES / ___ / Explain _____ ! NO / ___ / Explain _____
! _____
! _____
! _____

Investigation #2 !

YES / ___ / Explain _____ ! NO / ___ / Explain _____
! _____
! _____
! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / /

NO / X /

If yes, explain: _____

 / S / 7/28/97
Signature _____ Date _____
Title: CSO

 / S / 7/27/97
Signature of Office/ _____ Date _____
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 21045 **Trade Name:** LEVONORGESTREL 0.75MG TABLETS
Supplement Number: **Generic Name:** LEVONORGESTREL 0.75MG TABLETS
Supplement Type: **Dosage Form:** TAB
Regulatory Action: AP **Proposed Indication:** Emergency Contraception

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Does Not Apply

Formulation Status -

Studies Needed -

Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This has not been studied for pediatric use. Safety and efficacy in pediatric patients of reproductive potential are expected to be the same.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JENNIFER MERCIER

Signature

JS/

Date

7/28/99

A. DEBARMENT CERTIFICATION

In accordance with the provisions of §306(k) (21 U.S.C. §336) the applicant certifies that no services of any person debarred under §306(a) or (b) were or will be used in connection with this application.

MEMORANDUM

Date: February 3, 1999

To: File

From: Dr. Lisa Stockbridge
Regulatory Reviewer 
HFD-40

Re: Levonorgestrel Emergency Contraceptive ("Plan B")
Women's Capital Corporation
NDA 21-045 (MACMIS 7581)

This NDA was submitted to HFD-580 on January 29, 1999. On February 1, 1999, a proposed press release was faxed to DDMAC for review and comment. HFD-580 was consulted regarding appropriate risk information for this product. The NDA had not yet been filed, but it is believed that there are few side effects outside of nausea. All adverse events, including nausea, have less than 5% occurrence.

On February 3, 1999, I phoned Dr. Sharon Camp (President of Women's Capital Corporation) with two minor comments regarding the proposed press release. First, the press release would be lacking in fair balance because there was no risk information. It was suggested that the possibility of experiencing nausea be added to the press release for balance. Second, the third paragraph in the press release would be misleading because the claim that a use for the new drug is to prevent unintended pregnancy after unprotected sex would imply that this drug may be used as an alternative to conventional forms of contraception.

Dr. Camp stated that she would amend the press release and send it to press today. She also stated that she intends to create a joint proposal with Gynetics (Preven Emergency Contraceptive) to have the labeling changed to read that these emergency contraceptives may be used for contraceptive accidents or unprotected sex. She stated that "unprotected sex" refers to such instances as rape and is not misconstrued by consumers to mean that it is a substitute for other forms of contraception. She said that she has studies that have examined this interpretation.

cc: NDA 21-045
HFD-040/Stockbridge/Abrams/Ostrove

MEMORANDUM DEPARTMENT OF HEALTH AND
HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: February 23, 1999

To: David LePay, M.D., Director, Division of Scientific Investigations, HFD-340

From: Lana L. Pauls, M.P.H., Associate Director, Division of Reproductive and Urologic Drug
Products
(DRUDP; HFD-580)

Subject: Request for Clinical Inspections for NDA 21-045

In support of the above mentioned NDA for levonorgestrel tablets, the sponsor The Women's Capitol Corporation has submitted the results of the following pivotal protocols:

<u>Indication</u>	<u>Pivotal Protocol #</u>	<u>Investigator's Name/Address</u>
Prevention of Pregnancy	WHO/HRP study 92908	Mitchell Creinin, M.D. Pittsburgh PA Rosemary Kirkman, M.D. Manchester England Ding Ju-hong, M.D. Nanjing, China

We have discussed this application with Dr. Turner and as a result identified the above protocols/sites for inspection.

We have requested the international inspections because:

- There are insufficient domestic data; or
- Only foreign data are submitted to support an application; or
- Domestic and foreign data show conflicting results pertinent to decision-making; or
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations.
- Other: see attached memo.

We request that the inspections be performed and the Inspection Summary Results be provided by June 1, 1999. We intend to make a regulatory decision on this application by July 29, 1999.

Should you require any additional information please contact Ms. Christina Kish at 7-4271.

Concurrence:

Medical Team Leader: Dr. Slaughter

Medical Reviewer: Dr. Davis

cc:

Orig. NDA

HFD-580/Division File

HFD-580/CKish/LPauls/LRarick

HFD-344/GTurner

101
Filing Memo

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA 21-045

Drug/Drug Product: Levonorgestrel 0.75 mg oral tablets

Indication: Emergency Contraceptive

Date of Application: 1/29/99

Classification: Priority (3P)

PDUFA Goal Date: 7/29/99

Sponsor: Women's Capital Corporation (WCC)

PM (Kish), MO (Davis), Chem (Lin), Pcol (Jordan), Stat (Kammerman), PK (Parekh)

The NDA contains clinical safety and efficacy data from 2 well controlled randomized clinical studies on levonorgestrel for emergency contraception. Supporting data is also provided from 3 additional multicenter studies with 0.75 mg levonorgestrel and 32 additional single center studies with various doses. This product is intended to 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.

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 study and most other clinical studies in the NDA.

'Drug product 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'. (p. 030023, vol 1.1).

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

1. Relative bioavailability study to a micronized suspension, single dose
2. Three published studies, either as single (comparison to other product) or multiple dose (7 days).

Age Effects: age range for women in these studies is 19-44. This is the target population

therefore, formal age effects have not been studied (the reviewer can characterize over this this 2 fold age range, whether there is age related changes in pk).

Ethnicity: Caucasians and Africans were used in the relative bio study (N=9 and 6 resp). The studies in China are expected in Asian females. A pk analysis will be conducted by the reviewer to assess changes related to ethnic difference. Results will be assessed in light of safety and efficacy.

Special Populations: No formal renal or hepatic studies have been conducted in these populations but the sponsor states that since this would be an acute administration, this may not be critical.

Analytical Methods have been provided.

In-vitro dissolution has been provided.

Review Issues:

1. Formulations and dates of manufacture for all studies, literature and company sponsored.
2. Two tablets as per proposed regimen have not been studied although published data from q.d. administration has been provided. This too can be handled in the review since the question will be that of accumulation and safety. Since this has been studied in the trials, this issue can be handled by simulations.
3. Since some published data has been submitted in support of the pk studies, we should look at the complete literature search. Can the sponsor provide a listing? (Or we could do it ourselves).
4. The issues of 5% overage in the clinical formulations and the change with respect to starch had been addressed at previous meetings with the FDA. These will be considered and addressed during the review

The NDA 21-045 is fileable from Clinical Pharmacology and Biopharmaceutics perspective..

IS/ 2/17/99
Ameeta Parekh, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date - April 27, 1999
From Janet Woodcock, M.D.
Subject "Plan B" Trade Name

To Murray Lumpkin, M.D.
James Bilstad, M.D.
✓ Lisa Rarick, M.D.
Daniel Boring, M.D.

I received an appeal of the denial of the trade name "Plan B" for the emergency contraceptive product levonorgestrel (NDA 21-045). I reviewed the documentation in the case, and consulted with DDMAC on the consumer research that was done for the firm, and I find that the trade name is acceptable. The reasons are detailed below.

The phrase "plan B" in ordinary usage denotes an emergency or backup plan – something to employ when "plan A" fails. This common usage does not connote superiority or inferiority; rather, it implies a sequence or order. That emergency contraception should be a backup or emergency plan, not the primary method, is a useful public health message that is reinforced by the name of the product.

Many therapies in medicine have a sequential component to their indications; i.e., "indicated in patients who have failed . . ." While this failure is usually a judgement of the physician managing the patient, the emergency contraception scenario is unusual in that only the individual woman is in a position to recognize when "plan A" has failed and the need for emergency contraception is triggered. Therefore it is of utmost importance that the individual consumer thoroughly understand the role and timing of this intervention.

I think this name will be helpful to women, and do not believe it will mislead those who, due to cultural factors, do not understand the vernacular usage.

cc: Bob Temple
Jim Morrison
Janice Sheehy

Chemistry and Manufacturing Controls

Filing Meeting for NDA 21-045

February 17, 1999

David Lin

Levonorgestrel tablet; 0.75 mg
for emergency contraception
Sponsor: Women's Capital Corporation

Drug Substance

1. Levonorgestrel, USP is manufactured by _____ Manufacturing information is contained in DMF _____ This DMF was last reviewed in March, 1997 and found to be adequate to support an ANDA. An update to this DMF was submitted in July, 1998 and will need to be reviewed for this NDA.
2. The drug substance is released by _____ according to the following USP tests: 1) appearance, 2) identification by IR, 3) identification by specific rotation, 4) identification by melting range, 5) loss on drying, 6) residue on ignition, 7) chromatographic purity by _____ and 8) assay. The following additional tests will be performed: 1) particle size distribution, and 2) residual solvents by _____
3. Stability data are in the DMF.

Drug Product

1. The drug product is a tablet that contains levonorgestrel as the active component and other inactive components listed below.
2. The components and composition of the tablet are:

Component	Amount (mg/tablet)	Function
✓Levonorgestrel, USP	0.75	Active
✓Colloidal silicon dioxide, NF		Glidant
✓Potato starch		Binder
✓Magnesium stearate, NF		Lubricant
✓Gelatin, NF		Binder
✓Talc, USP		Glidant
✓Corn starch, NF		Diluent
✓Lactose monohydrate, NF		Diluent
		Solvent
		Solvent
		Solvent
Total		

3. Site of manufacturing and control, primary packaging, stability studies:

4. Site of quality control testing before secondary packaging:

5. The product tablets will be packaged in a two-count blister package configuration. Secondary packaging is conducted by

6. Primary Stability data (for tablets manufactured before plant renovations):
 - a. 3 full-scale batches of bulk tablets:

25°C/60% RH	(3, 6, 10, 12 months)
40°C/75% RH	(3, 6, 9 months)

 - b. 4 full-scale batches (2 batches from the above bulk tablets) packaged in 4-count blisters:

25°C/60% RH	(up to 20, 9, 16, and 16 months)
40°C/75% RH	(3, 6 months)

 - c. 3 full-scale batches packaged in 10-count blisters:

25°C/60% RH	(up to 48 & 60 months)
40°C/75% RH	(3, 6 months)

Tests performed: 1) assay, 2) disintegration, 3) dissolution, and 4) related substances.

7. Primary Stability data (for tablets manufactured after plant renovations):
 - a. 4 full-scale batches packaged in 2-count blisters:

25°C/60% RH	(up to 2, 2, 2, and 6 months)
30°C/60% RH	(up to 2, 2, 2, and 6 months)
40°C/75% RH	(up to 2 months)

Dissolution testing failure after 2 months at 40°C/75% RH.

- b. 3 full-scale batches packaged in 42-count blisters (packaged by)

25°C/60% RH	(up to 6 months)
40°C/75% RH	(up to 3 months)

Dissolution testing failure after 6 months at 25°C/60% RH and 3 months at 40°C/75% RH.

Tests performed: 1) assay, 2) disintegration, 3) dissolution, and 4) related substances.

8. The sponsor has not proposed an expiration dating period but recognizes that with the limited data submitted this period might be 6 months or less.

9. EA: The firm has requested a categorical exclusion.

10. Labeling: The tradename, Plan B, has been determined by the Labeling and Nomenclature Committee to be unacceptable.

Conclusion:

The CMC section of the NDA is not very well organized. However, the information presented is suitable for review.

This NDA may be filed from the CMC point of view.

cc:

NDA 21-045 Division File

HFD-580/CKish

HFD-580/MJRhee/DLin

MERCIZ

Teleconference Minutes

Date: July 15, 1999 **Time:** 11:20 p.m. EDT **Location:** Parklawn, 17B-45
NDA 21-045 **Drug:** Plan B **Indication:** emergency contraception
Sponsor: Women's Capital Corporation
Type of Meeting: Guidance
Meeting Chair: Ameeta Parekh, PhD
External Lead: Sharon Camp, PhD
Meeting Recorder: Kim Colangelo, BS

FDA Attendees:

Ameeta Parekh, PhD – Clinical Pharmacology and Biopharmaceutics Team Leader, Division of
Pharmaceutical Evaluation II (DPE II) @ DRUDP (HFD-580)
Kim Colangelo, BS - Regulatory Project Manager, DRUDP (HFD-580)

External Attendee:

Sharon Camp, PhD – President, Women's Capital Corporation

Meeting Objective: To convey general comments from the Clinical Pharmacology and
Biopharmaceutics review of the Plan B NDA; these comments are not requested as
Phase 4 commitments, nor are they approvability issues.

Discussion:

- information is lacking regarding the isozymes responsible for the metabolism of levonorgestrel and about potential drug interactions; *in vitro* metabolism studies, followed by appropriate *in vivo* drug interaction studies, are recommended; guidance on *in vitro* studies is available on the internet at www.fda.gov/cder
- based on the information submitted, a potential difference in the efficacy in the Asian population was noted; pharmacokinetic studies to explore potential racial differences are recommended; if studies demonstrate relevant differences between racial groups, revised dosing instructions may be considered

Decisions:

- sponsor agrees that these issues are important, and will discuss the possibility of further research being conducted by another entity (e.g., World Health Organization); DRUDP is available for consultation on study design if desired

NDA 21-045
Teleconference Minutes 07.15.99
Page 2

Action Items:

- sponsor will inform agency of research developments regarding Plan B
- minutes of this teleconference will be forwarded to sponsor within 30 days

SI

Minutes Preparer

Concurrence, Chair

cc:
Original NDA 21-045
HFD-580/DivFile
HFD-580/Mercier/Rumble/Rarick/Mann/Parekh

drafted: Colangelo, 07.15.99
concurrence: Parekh, Rumble, 07.15.99
final: Colangelo, 07.15.99

MINUTES

Moose

Meeting Minutes

Date: June 11, 1999 **Time:** 4:00-5:00 PM

Location: Parklawn; 17B-43

NDA 21-045

Drug: Plan B™ (levonorgestrel)

Indication: Emergency Contraception

Sponsor: Women's Capital Corporation

Type of Meeting: Labeling

Meeting Chair: Marianne Mann, M.D.

External Lead: Sharon Camp, M.D.

Meeting Recorder: Jennifer Mercier, B.S.

FDA Attendees:

Marianne Mann, M.D. – Deputy Director, Division of Reproductive and Urologic Drug Products; (DRUDP; HFD-580)

Daniel Davis, M.D. – Medical Officer, DRUDP (HFD-580)

Lisa Stockbridge – Regulatory Reviewer, Division of Drug Marketing, Advertising, and Communications (DDMAC) HFD-040

Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

Sharon Camp, M.D. – Women's Capital Corporation

Meeting Objective: To discuss the final physician package insert.

Decisions made:

- see attached label
- WCC cannot compare PLAN B™ to Preven™ in marketing campaigns
- only what is stated in the label may be marketed
- the label states that PLAN B™ is "at least as effective as the Yuzpe regimen in preventing pregnancy"
- claims of superiority can only be made concerning nausea and vomiting
- carton label needs to be identical in wording to patient package insert if wording is desired; alternatively, the sponsor may wish to pursue providing such information with DDMAC post-approval as an attachment to the carton

Unresolved decisions:

- Patient package insert wording

Action Items:

- the patient package insert and the carton label should be submitted for review

Meeting Minutes

Date: July 9, 1999

Time: 12:00 - 1:00 PM

Location: Parklawn; 18B-37

NDA 21-045

Drug: PLAN B™ (levonorgestrel) 0.75 mg Tablets

Indication: Emergency Contraception

Sponsor: Women's Capital Corporation

Type of Meeting: Labeling and Chemistry issues

Meeting Chair: Marianne Mann, M.D.

External Lead: Sharon Camp, Ph.D.

Meeting Recorder: Jennifer Mercier, B.S.

FDA Attendees:

Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP ; HFD-580)

Daniel Davis, M.D. - Medical Officer, DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D. - Team Leader, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)

David Lin, Ph.D. - Chemist, DNDCII @ DRUDP (HFD-580)

Ameeta Parekh, Ph.D. - Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Jennifer Mercier, B.S. - Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

Sharon Camp, Ph.D. - Women's Capital Corporation

Gordon Duncan, M.D. - Women's Capital Corporation

Meeting Objective: To discuss the final label and the chemistry information submitted on July 6, 1999.

Background: The Division and the sponsor agreed to accept additional stability data to review to possibly extend the expiration date that is current agreed upon. The information was submitted on July 6, 1999. This information was actually a major amendment to the NDA.

Decisions made:

- The information submitted July 6, 1999 is proposing new calculation for the data, this is considered a major amendment.
- The Division agrees to a 8 month expiration dating of this product because of the limited data and product failure at 2 months at 40°

NDA 21-045
Meeting Minutes
Page 2

- The sponsor has the option to accept the expiration dating of 8 months or the review clock can be extended the 3 months to review the additional data that they supplied on July 6, 1999.
- A supplement with additional stability data to extend the expiration dating can be discussed after the action of this NDA
- The sponsor is suggested to review the stability guidelines before the supplement is submitted
- The sponsor may request a meeting to discuss the supplement and what the Division would require

Unresolved decisions: None

Action Items:

- Fax meeting minutes to sponsor within 30 days

Minutes Preparer

Concurrence, Chair

cc:

Original NDA

HFD-580/DivFile

HFD-580/Rumble/Mercier

HFD-580/Rarick/Mann/Davis/Rhee/Lin/Parekh

drafted: July 20, 1999/Mercier

concurrence:

final:

MEETING MINUTES

Meeting Minutes

Date: May 3, 1999 **Time:** 2:00 – 3:00 PM **Location:** Parklawn; 17B-43

NDA 21-045 **Drug:** Plan B (levonorgestrel) **Indication:** Emergency Contraception

Sponsor: Women's Capital Corporation

Type of Meeting: Status Meeting (Internal)

Meeting Chair: Marianne Mann, M.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:

Marianne Mann, M.D. – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Shelley Slaughter, M.D., Ph.D. ng Team Leader, DRUDP (HFD-580)

Daniel Davis, M.D. – Medical Officer, DRUDP (HFD-580)

David Lin, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)

David Hoberman, Ph.D. – Biostatistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Ameeta Parekh, Ph.D. – Biopharmaceutics Team Leader, Division of Clinical Pharmacology and Biopharmaceutics II (DPBII) @ DRUDP HFD(580)

Terri Rumble - Chief, Project Management Staff, DRUDP (HFD-580)

Jennifer Mercier - Project Manager, DRUDP (HFD-580)

Meeting Objective: To establish the status of reviews for this pending NDA.

Decisions made:

Clinical

- review will be completed approximately May 15, 1999
- the efficacy in Asian women should be reviewed for the blood levels in the PK studies

Biopharmaceutics

- review is in progress; reviewer is aware of the June 15, 1999 goal date
- examples of acceptable labels for comparison should be communicated to the sponsor

Chemistry

- review is in progress; reviewer is aware of the June 15, 1999 goal date
- there are stability problems that are effecting the expiration dating of the product

Statistics

- review is in progress; reviewer is aware of the June 15, 1999 goal date
- review data on claims for less nausea

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Pharmacology

- review is in progress; reviewer is aware of the June 15, 1999 goal date

Unresolved decisions: None

Action Items:

- Dr. Parekh will locate appropriate label for comparison

/S/

Minutes Preparer

/S/

Concurrence, Chair

cc:

Original IND

HFD-580/DivFile

HFD-580/PM/Rumble/Pauls/Mercier

HFD-580/Rarick/Mann/Slaughter/Allen/Davis/Jordan/Rhee/Lin/Kammerman/Parekh

drafted: May 5, 1999/Mercier

concurrence: May 7, 1999/Rumble

final:

MEETING MINUTES

DIN

Teleconference Minutes

Date: April 29, 1999 Time: 2:00-2:30 PM

Location: Parklawn; 17B-45

NDA 21-045

Drug: Levonorgestrel

Indication: Emergency Contraception

Sponsor: Women's Capital Corporation

Type of Meeting: Request for availability of information

Meeting Chair: Marianne Mann, M.D.

External Lead: Sharon Camp

Meeting Recorder: Jennifer Mercier

FDA Attendees:

Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Products; DRUDP (HFD-580)

Jennifer Mercier - Project Manager, DRUDP (HFD-580)

External Attendees:

Sharon Camp, Women's Capital Corporation

Meeting Objective: To convey two questions and ascertain the availability of information to be submitted to the FDA.

Decisions made: (questions)

1. How many original case report forms (CRFs) are available from each site?

- All CRFs are available to submit to the FDA.

2. Did all patients receive the same dosing instructions?

- All patients were given the same dosing instructions except the _____ facility because of a convenience factor.

Unresolved decisions: None

Action Items:

- fax meeting minutes to sponsor within 30 days

JSI

Minutes Preparer

JSI

Concurrence, Chair

5/5/99

**NDA 21-045
Meeting Minutes
Page 2**

cc:

**Original IND
HFD-580/DivFile
HFD-580/PM/Rumble/Mercier
HFD-580/Rarick/Mann/Davis/**

**drafted: May 3, 1999/Mercier
concurrence: May 4, 1999/Rumble
final: May 5, 1999/Mann/Rumble**

MEETING MINUTES

DIV

Meeting Minutes

Date: April 26, 1999 **Time:** 10:30- 12:00 PM **Location:** Parklawn; 17B-43
NDA 21-045 **Drug:** Levonorgestrel **Indication:** Emergency Contraception

Sponsor: Women's Capital Corporation

Type of Meeting: CMC Discussion

Meeting Chair: Lisa Rarick, M.D.

Meeting Recorder: Jennifer Mercier

External Lead: Sharon Camp

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products
(DRUDP; HFD-580)

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II
(DNDCII) @ DRUDP (HFD-580)

David Lin, Ph.D. - Chemist, DNDCII @ DRUDP (HFD-580)

Terri Rumble - Chief, Project Management Staff, DRUDP (HFD-580)

Jennifer Mercier - Regulatory Project Manager, DRUDP (HFD-580)

External Participants:

Sharon Camp, Women's Capital Corporation

Gordon Duncan, Women's Capital Corporation

Karin Kook, Women's Capital Corporation

Andres Pap, Women's Capital Corporation

Meeting Objective: To discuss the Chemistry issues regarding stability and expiration for the pending application for emergency contraception sponsored by Women's Capital Corporation.

Discussion: (Questions)

1. Could WCC expect a 24-month expiration dating period? If not, what expiration dating period for the drug product can WCC expect? Are there labeling changes (relative to storage conditions) WCC could make which would permit a longer expiration dating period?

- This would depend on review of the data.

2. a. Understanding that the plants will close this summer after the FDA inspection, but most likely prior to FDA approval of the proposed levonorgestrel emergency contraceptive, does the FDA have any special guidance with respect to WCC's plans to produce commercial product for the U.S. market in the existing facilities?
- The FDA does not have any special guidances regarding WCC's plans but can provide the The Scale-Up and Post Approval Changes (SUPAC) Guidance.
- b. Will a site-change supplement be required post-approval for approval of the renovated/relocated formulation plant? Is anything required for the packing plant relocation on the
- Yes, a supplement would be required post-approval for both the renovated/relocated formulation plant and the packaging facility.
- c. If a site-change supplement is required:
- Will additional stability data will be required?
 - Will a bioequivalence study be required?
 - Will an inspection of either or both of the "new" plants be required prior to commercial production from that area? What can WCC expect in terms of a timetable for inspections of the new area?
- The site-change supplement will have to include additional stability data and possibly a bioequivalence study depending upon the nature of the changes. An inspection would have to be conducted on both of the new sites prior to commercial production.
3. The expiration dating period would be on all shipping containers for drug product imported from and included on each secondary package. Since the NDA, the proposed commercial label includes an expiration dating period on the blister card, WCC plans to request a variance relative to the proposed commercial label for the blister card. Would this plan be acceptable to the Division?
- Expiration dating should be permanently affixed to all secondary packaging. If the blister card is sandwiched between the permanent cardboard such that it cannot be easily removed, then this proposal is acceptable.

Chemistry Issues:

- After renovation of the manufacturing site the drug product has shown a stability problem during accelerated conditions per the ICH Guidelines (40°C/ 75% RH storage) that did not exist with the previously manufactured product
- monitoring of the temperature will be done to insure drug product is kept at 25° - 30°C during shipping
- multiple changes in manufacturing make it difficult to pinpoint the stability problem
- testing on bulk product using the old manufacturing process and comparing the results with the current manufacturing process results may reveal the cause of the problem in the stability of the drug product
- stability testing will be on-going

- a major amendment to the NDA, during the last 90-days of the PDUFA clock, will result in an extension of the review clock by 3 months
- the expiration dating at the time of an action is a tentative one and will be confirmed by stability testing the commercial batches
- dissolution specification may need to be modified

Unresolved decisions: None

Action Items:

- fax meeting minutes to sponsor within 30 days
- the sponsor will inform DRUDP as to their business decision regarding whether the stability data will be submitted as a major amendment prior to action or submitted after action

/S/

Minutes Preparer

Concurrence, Chair

cc:

Original NDA

HFD-580/DivFile

HFD-580/PM/Rumble/Mercier

HFD-580/Rarick/Mann/Rhee/Lin

drafted: April 27, 1999/Mercier

concurrence: April 29, 1999/Rumble

final:

MINUTES

Meeting Minutes

Date: April 22, 1999 **Time:** 2:30 – 3:00 PM **Location:** Marianne's Office

NDA 21-045 **Drug:** Levonorgestrel **Indication:** Emergency Contraception

Sponsor: Women's Capital Corporation

Type of Meeting: CMC Discussion (Internal)

Meeting Chair: Lisa Rarick, M.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:

Lisa Rarick, M.D. – Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Marianne Mann, M.D. – Deputy Director, DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)

David Lin, Ph.D. – Chemist, DNDCII @ DRUDP (HFD-580)

Christina Kish – Project Manager, DRUDP (HFD-580)

Jennifer Mercier – Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the Chemistry issues regarding stability and expiration for the pending application for emergency contraception sponsored by Women's Capital Corporation.

Discussion: (Questions)

1. Could WCC expect a 24-month expiration dating period? If not, what expiration dating period for the drug product can WCC expect? Are there labeling changes (relative to storage conditions) WCC could make which would permit a longer expiration dating period?

- This would depend on the review of the data.

2. a. Understanding that the plants will close this summer after the FDA inspection, but most likely prior to FDA approval of the proposed levonorgestrel emergency contraceptive, does the FDA have any special guidance with respect to WCC's plans to produce commercial product for the U.S. market in the existing facilities?

- The FDA does not have any special guidances regarding WCC's plans. We will provide the SUPAC guidance.

b. Will a site-change supplement be required post-approval for approval of the renovated/relocated formulation plant? Is anything required for the packing plant relocation on the

- Yes, a supplement would be required post-approval for both the renovated/relocated formulation plant and the packing plant.
- c. If a site-change supplement is required:
 - Will additional stability data will be required?
 - Will a bioequivalence study be required?
 - Will an inspection of either or both of the "new" plants be required prior to commercial production from that area? What can WCC expect in terms of a timetable for inspections of the new area?
- The site-change supplement will have to include additional stability data and depending upon the nature of the change involved a bioequivalence study may be needed. An inspection would have to be conducted on both of the new sites prior to commercial production.
- 3. The expiration dating period would be on all shipping containers for drug product imported from _____ and included on each secondary package. Since the NDA, the proposed commercial label includes an expiration dating period on the blister card, WCC plans to request a variance relative to the proposed commercial label for the blister card. Would this plan be acceptable to the Division?
 - The Division does not find this proposal as written acceptable, but will clarify the question at the meeting with the sponsor.

Unresolved decisions: None

Action Items:

- Communicate decisions to sponsor at the meeting on April 26, 1999.

/s/

Minutes Preparer

Concurrence, Chair

cc:

Original NDA

HFD-580/DivFile

HFD-580/PM/Rumble/Mercier

HFD-580/Rarick/Mann/Rhee/Lin

drafted: April 22, 1999

concurrence: April 26, 1999/Rumble

final: May 4, 1999/Rarick/Mann/Rhee/Lin

MINUTES

Status Meeting Minutes

Date: April 5, 1999 Time: 3:30 PM - 4:30 PM Location: Parklawn C/R 17B-43

NDA 21-045 Drug Name: levonorgestrel 0.75 mg tablets

Type of Meeting: status meeting (internal)

Meeting Chair: Christina Kish

Meeting Recorder: Christina Kish

FDA Attendees:

Shelley Slaughter, M.D., Ph.D. - Medical Officer Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)

Dan Davis, M.D. - Medical Officer, DRUDP (HFD-580)

Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

David Hoberman, Ph.D. - Mathematical Statistician, Division of Biometrics I (HFD-710)

David Lin, Ph.D. - Chemist, DNDCII @ DRUDP (HFD-580)

Terri Rumble, B.S.N. - Chief, Project Management Staff, DRUDP (HFD-580)

Christina Kish - Project Manager, DRUDP (HFD-580)

Meeting Objectives:

To discuss the status of reviews for this pending new drug application.

Discussion Points:

- Background
 - the sponsor, the Women's Capitol Corporation, submitted a new drug application for a levonorgestrel only emergency contraceptive
 - this application was filed on March 31, 1999
 - the final goal date for this application is July 29, 1999
 - the Division goal date for this application is June 15, 1999
- Clinical
 - the review is currently ongoing
 - the reviewer will be ready to discuss review parameters with statistics in two weeks
 - the review is expected to be completed the first week in June
- Statistical
 - the review will initiated within the next two weeks
 - the reviewer will be ready to discuss review parameters with clinician in two weeks
 - the review can be completed by the first week in June

- **Chemistry, Manufacturing and Controls**
 - the DMF appears acceptable
 - stability will be a major review issue
 - inspection of the manufacturing sites is scheduled for the end of May
- **Biopharmaceutics**
 - the review is expected to be initiated next week
 - a literature review in support of the pharmacokinetic data is currently being conducted by the FDA library
 - the review is expected to be completed before the first week in June
- **Tradename**
 - the sponsor submitted the tradename "Plan B" for this application
 - the labeling and nomenclature committee considered this tradename and did not find it acceptable
 - the Division concurred with this and the decision was communicated to the sponsor
 - the sponsor appealed the decision at the Division and Office level; both times the original decision not to accept the tradename was upheld
 - the sponsor appealed to Dr. Lumpkin who also upheld the decision
 - the sponsor currently is appealing to Dr. Woodcock; Center Director, a decision has not yet been rendered
 - should the sponsor be required to propose another tradename for this product, they have a proposed tradename of "Afina." However, they prefer their original tradename and will only put "Afina" forward as a last resort
 - the initial reaction from the LNC to this tradename is that it will also be problematic due to several look alike, sound alike tradenames already on the market

Decisions Reached:

- a working meeting between statistics and clinical reviewers should be set up within the next two weeks
- labeling comments, if completed early, can be provided to the Project Manager before the labeling meetings scheduled for June 7, 1999

Unresolved Issues: none

Action Items: see decisions reached

/S/

Minutes Preparer

4/14/99

/S/

Concurrence, Chair

4/14/99

NDA 21-045
levonorgestrel 0.75 mg
April 5, 1999

Page 3

cc:

Orig.

HFD-580

MEETING ATTENDEES

HFD-580/CKish/4.5.99/n21045.im2

Concurrence: TRumble 4.6.99/DLin 4.7.99/SSlaughter 4.13.99/DDavis 4.13.99

MEETING MINUTES

MEETING MINUTES (Filing Meeting)

Date: February 17, 1999
17B-43

Time: 2:00 - 3:00 PM

Location: Parklawn; Room

NDA: 21-045

Drug Name: PROPRIETARY NAME (levonorgestrol) for
emergency contraception
Women's Capital Corporation (WCC)

Type of Meeting: Internal Filing Meeting

Meeting Chair: Lana L. Pauls, M.P.H..

External Participant Lead: none

Meeting Recorder: Lana L. Pauls, M.P.H.

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Lana L. Pauls, M.P.H. Associate Director, DRUDP (HFD-580)

Dan Davis, M.D. - Medical Officer, DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II
(DNDC II) @ DRUDP (HFD-580)

David Lin, Ph.D. - Chemist, DNDCII @ DRUDP (HFD-580)

Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

David Hoberman, Ph.D. - Mathematical Statistician, DBII @ DRUDP (HFD-580)

Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Division of Pharmaceutical Evaluation II
(DPE II) @ DRUDP (HFD-580)

Background:

This NDA was received on January 29, 1999. It has been classified as a priority application. Therefore, if filed, the User Fee Goal Date is July 29, 1999.

Meeting Objectives:

To determine whether this application can be filed.

Discussion Points:

Clinical

- acceptable for filing
- one, large randomized trial conducted (~ 2000 women in 14 Countries)

- the trial was designed to claim "as good as" in terms of efficacy in comparison to the "Yutzpe regimen"

Pharmacology

- acceptable for filing

Chemistry

- acceptable for filing
- EER sent
- the proposed proprietary name, Plan B, is unacceptable; the applicant has appealed the decision by the nomenclature committee to Mac Lumpkin

Biopharmaceutics

- acceptable for filing
- details regarding the formulations used in the PK studies (including published literature) should be requested from the applicant, if possible
- a complete listing of the literature for PK studies should be requested from the applicant

Statistics

- acceptable for filing

Clinical Site Selection

- will be selected no later than February 19, 1999; Dan will work with Chris and Lana regarding memo to be sent to DSI (at least one foreign site will be required)

Unresolved Issues: none

Action Items:

Item:	Responsible Person:	Due Date:
• select sites for DSI	Dan Davis/Chris Kish	02/19/99
• prepare DSI memo	Lana Pauls	02/22/99

Signature, minutes preparer

Concurrence, Chair

NDA 21-045
PROPRIETARY NAME (levonorgestrol)
Meeting Minutes - February 17, 1999

Page 3

cc:

NDA Arch:

HFD-580

HFD-580/JMercier/Attendees

HFD-580/LPauls/02.17.99/WCC_filing

Concurrences:

DDavis, MRhee, DLin 02.24.99/LKammerman 03.01.99/DHoberman 03.02.99/AParekh 03.03.99

No response received from:

APPEARS THIS WAY
ON ORIGINAL