**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 2-843**

# MEDICAL REVIEW(S)

Moore

FEB 25 1998

NDA 20-843

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# Medical Officer's Review
## (Original Review)

| | |
|---|---|
| **Sponsor:** | **Schering Corporation<br>Galloping Hill Road<br>Kenilworth, N. J. 07033** |
| **Drug:** | |
| **Generic:** | **Progesterone, USP** |
| **Trade:** | **Prometrium®** |
| **Chemical:** | **Pregn-4-ene-3, 20 dione** |
| **Route:** | **Oral** |
| **Dosage Form:** | **Soft Gelatin Capsule** |
| **Strength:** | **100 mg** |
| **Proposed indication:** | **Prevention of endometrial hyperplasia in non-hysterectomized post-menopausal women who are receiving conjugated estrogens tablets** |
| **Related NDAs:** | **NDA 19-781 (Prometrium Capsules for use in secondary amenorrhea)** |
| **Related Documents:** | ***Minutes of Meetings* dated: 5/30/95, 12/7/95, 8/28/96, 11/1/96, 4/8/97, 5/7/97<br>*Minutes of Teleconferences* dated: 2/4/97, 2/11/97<br>*Memorandum from PEPI Coordinating Center* dated: 6/20/97** |

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1. Resume

**In support of safety and efficacy of micronized progesterone (MP) administered in combination with conjugated equine estrogen (CEE) as a component of combination estrogen-progestin hormone replacement therapy (HRT) for the prevention of endometrial hyperplasia in postmenopausal women with a uterus, the sponsor has submitted the results of one adequate, well-controlled, pivotal Phase III clinical trial, the Postmenopausal Estrogen/Progestins Interventions (PEPI) Trial which was sponsored by the National Institutes of Health under a research project cooperative agreement (IND At the meeting with the Division, the sponsor received agreement that the PEPI trial was acceptable to use as the only pivotal Phase III study to support the indication and that the 200 mg dose was acceptable. An additional dose ranging study was not required. A drug interaction study would be required and in November 1996 agreement was obtained that this required study would be underway at the time of the NDA submission. After filing, the Division was notified that the required drug interaction study had not begun.**

**The PEPI Trial, conducted between December 27, 1989 and April 1, 1994, was a prospective, randomized, double-blind, placebo-controlled, multicenter trial with 3 years of treatment conducted to assess the influence of estrogen, with and without a progestin, on heart disease risk factors including high-density lipoprotein, cholesterol, fibrinogen, insulin, and blood pressure in 875 women (596 with a uterus and 279 without a uterus). The trial also offered a unique opportunity to study the effects of hormone replacement therapies on the endometrium. The histological findings of the endometrium of 596 women with a uterus who were randomly assigned to placebo, estrogen-only, or one of three estrogen plus progestin regimens (CEE plus cyclic medroxyprogesterone acetate [MPA], CEE plus continuous MPA, and CEE plus cyclic MP) were reviewed and reported upon. Trial results provided adequate evidence that combining CEE with cyclic MP, or cyclic or continuous MPA, protected the endometrium from hyperplastic changes associated with estrogen-only therapy.**

**The primary efficacy endpoint for the Schering-Plough Research Institute (SPRI) data analysis was the worst endometrial histology assessment based of the endometrial biopsies in women with an intact uterus over the three year treatment period. Endometrial biopsies were performed at baseline and annually at 12, 24, and 36 months on all participants with a uterus. Biopsy results were classified as follows: no hyperplasia, simple (cystic) hyperplasia, complex (adenomatous) hyperplasia, atypical hyperplasia, and adenocarcinoma. Biopsies were evaluated locally, at each site, and centrally in a blinded manner. Where the two evaluations differed, an arbiter, again evaluated the results. The result rated for 2 of the 3 evaluators was considered the final result. If there was no agreement between the evaluators, the local rater made the determination as to which evaluation would be the final result.**

**The primary efficacy variable was the proportion of patients with any hyperplasia as the worst diagnosis during the three years of treatment. Incidence rates of hyperplasia were low in all treatment groups except the CEE alone group.**

**The secondary objectives of the SPRI data analysis of the PEPI Trial were to compare the safety and tolerability of MP+CEE versus CEE alone and with other active treatment regimens and placebo in women with and without a uterus which included comparing the effects of MP+CEE versus the other active treatment regimens and placebo on plasma lipoproteins, fasting and 2-hour postprandial plasma insulin and glucose levels, fibrinogen levels, blood pressure, and body weight.**

2. Background

2.1 Regulatory history

Micronized progesterone as Utrogestan® was first marketed overseas in 1980 by Besins-Iscovesco Pharmaceuticals, Inc. Since that time it has been marketed in 26 countries for various indications including menstrual irregularities

related to anovulation and dysovulation, luteal insufficiency, and postmenopausal hormone replacement therapy.

NDA 19,781 was submitted September 30, 1987 by Besins Pharmaceutical, Inc. for the treatment of secondary amenorrhea in premenopausal women. The reviewing medical officer felt that none of the submitted clinical studies supported the efficacy of the proposed doses of Utrogestan® for the claimed indication and recommended that the NDA not be filed. It was resubmitted March 17, 1989 by LaSalle Laboratories, US affiliate of Besins-Iscovesco Pharmaceuticals, Inc. Transfer of ownership of the NDA to Schering Corporation occurred July 1990. A not approvable letter was sent to Schering Corporation August 17, 1990 indicating that the application failed to provide substantial evidence of the efficacy of Urogestan® as claimed in the labeling; it failed to provide appropriate bioavailability and bioequivalence information, and the labeling submitted did not comply fully with 21 CFR 201.57. Subsequent to a response from the sponsor, concurrence was reached to address deficiencies by conducting two pharmacokinetic studies and an additional clinical trial to address the effectiveness of micronized progesterone (SCH 961) on inducing endometrial secretory transformation in postmenopausal women with proliferative endometrium induced by estrogen priming.

Schering Corporation resubmitted NDA 19, 781 February 8, 1996 and on November 12, 1996 committed to perform a Phase IV study to provide direct data on the pharmacokinetics, safety and efficacy of the 400 mg dose in the target population, and to compare the pharmacokinetics, safety and efficacy of the 300 mg and 400 mg doses. A revised labeling would be submitted incorporating data at the completion of the Phase IV study. An approvable letter was sent to Schering Corporation on March 28, 1997.

On March 12, 1997 Schering Corporation submitted an original new drug application for Prometrium Capsules, 100 mg to be administered orally for use in the prevention of endometrial hyperplasia in non-hysterectomized post-menopausal women who are receiving conjugated estrogens tablets. See Attachments 1 and 2 for a more detailed regulatory history of IND and NDA 20,843.

**2.2 Clinical implications of preclinical sections**

**2.2.1 Chemistry, Manufacturing and Control**

Please refer to Chemistry, Manufacturing and Control review. No safety issues were identified.

**2.2.2 Pharmacology/toxicology**

Please refer to Pharmacology review.

A well-designed oncogenicity study of progesterone by the oral route of administration in rodents has not been conducted. However, the results of a two-year dietary oncogenicity study of medroxyprogesterone acetate (MPA) in female rats demonstrated a dose-related increased incidence of pancreatic islet hyperplasia and tumors (adenomas and carcinomas) was seen at 1000 and 5000 mg/kg/day but not at 200 mg/kg/day.[1] The study sponsor and the FDA concurred that the increased incidence of pancreatic tumors was not believed to present a risk to humans because the rat endocrine system is generally more sensitive to hormonal imbalance than humans and when a progestin is combined with estrogen more progesterone receptors are produced and more receptors are available to bind the progestin (NDA 20,843, volume 1.7, section 3.E, page 2).

Both endogenous progesterone and synthetic progestins produce, to varying, degrees, the same pharmacologic responses. They combine with progesterone receptors in various tissues to produce their effects.[2] Micronized progesterone is identical to endogenous progesterone of ovarian origin, and oral administration of SCH 961 at the therapeutic dose for HRT produces blood levels of progesterone in the physiological range.

1. Wyeth-Ayerst Laboratories - Prempro™/Premphase™ Summary Basis of Approval NDA 20-303, (1994) Food and Drug Administration, Rockville, MD.

2. Williams CL and Stancel GM (1996). Estrogens and progestins. In: Hardman JG, Limbird LE (eds. in chief), Molinoff PB, Ruddon Rw (eds.) and Gilman AG (consulting ed.) Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th edition, McGraw-Hill, New York. pp. 1411-1440.

A single oral dose of 200 mg micronized progesterone given to postmenopausal women yielded plasma levels of 19-28 ng/ml progesterone, within the normal range of various physiological states: 10-20 ng/ml, found during the luteal phase of the menstrual cycle, and 52 ng/ml by the 20th week of pregnancy. Endogenous progesterone taken orally has a very short half-life due to extensive first-pass metabolism in the liver, while synthetic progestins have a much longer half-life.[2] These characteristics of SCH 961, per the sponsor, indicate that conducting further animal studies would not add to the human risk assessment for micronized progesterone.

**2.3 Human pharmacokinetics/bioavailability**
Please refer to Clinical Pharmacology and Biopharmaceutics review.

In response to the pharmacokinetic data deficiencies cited in the original NDA 19,781 (in a correspondence from the FDA dated August 17, 1990), Schering Corporation conducted two pharmacokinetic studies to evaluate the effect of food on the oral availability of progesterone from this soft gelatin capsule formulation, and to evaluate the multiple dose pharmacokinetic profile and dose proportionality of SCH 961. Healthy men constituted the study population in both studies. The administration of oral micronized progesterone with food or in a post-prandial state up to 4 hrs after a meal, in general, increased the bioavailability of SCH 961 although this effect was quite unpredictable exhibiting both high intersubject and intrasubject variability.[3] Steady state serum progesterone concentrations were attained within 7 days after once-a-day multiple dose oral administration.[4] Serum elimination half-life of progesterone was found to be independent of dose and ranged between 13 and 17 hours. [3,4]

**3. Description of clinical data source**
The clinical section of this application includes the study report of one clinical trial (Study H89-117) - the NIH-sponsored Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial: a 36 month, prospective, randomized, double-blind, placebo-controlled multicenter study of 875 women (596 with a uterus, 279 without a uterus) assigned to one of five blinded therapies. Schering-Plough supplied the micronized progesterone (MP, SCH 961) used in the PEPI Trial.

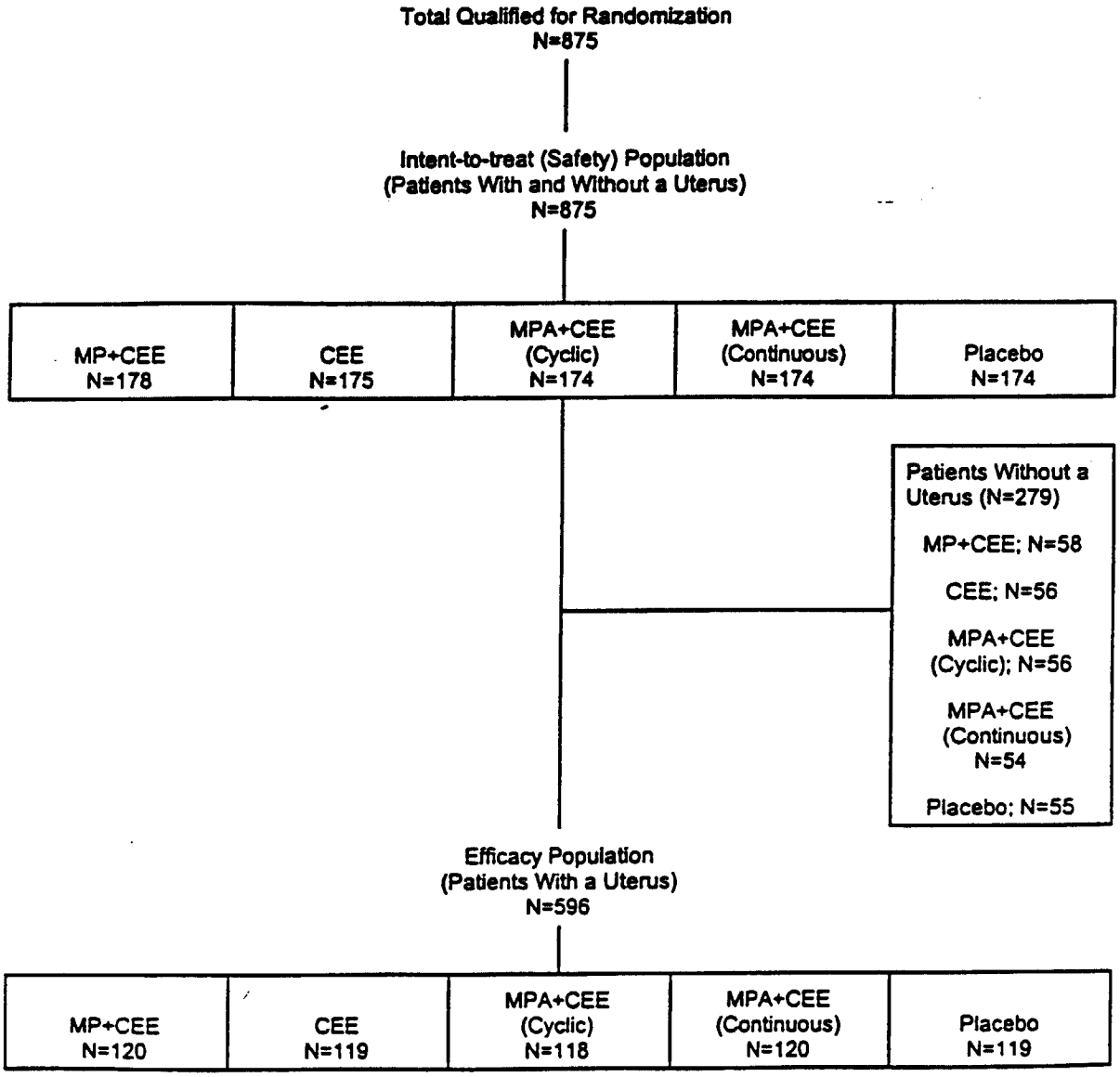
**4. Clinical trial H89-117**
**4.1 Objective/rationale**
The Schering-Plough Research Institute (SPRI) analyzed the data from the PEPI Trial to support the use of MP in combination with CEE as HRT. The primary objective of the SPRI data analysis is to determine the efficacy of MP 200 mg daily for the first 12 days of each 28-day cycle in combination with CEE 0.625 mg daily (MP + CEE) compared with CEE alone for the prevention of endometrial hyperplasia in women with a uterus. The effects of CEE alone, CEE in combination with different progestin agents and placebo on plasma lipoprotein (HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol, total cholesterol, and triglycerides), systolic and diastolic blood pressure, fasting and 2-hour postprandial plasma insulin and glucose levels, plasma fibrinogen, and body weight were assessed as secondary objectives. The evaluation of safety included adverse event assessments.

**4.2 Design**
The PEPI Trial was a prospective, randomized, double-blind, placebo-controlled, multicenter study in postmenopausal women. 875 eligible patients (596 with a uterus and 279 without a uterus) were randomized to one of five blinded therapies administered in 28-day cycles. Treatment group assignment was stratified by clinic center and patient's uterine status, and was assigned using a computer-generated randomization schedule developed by the PEPI Coordinating Center. See Figure 1.

3. SCH 961: A Study Evaluating the Effect of Food on the Oral Bioavailability of Prometrium®: A Four-Way Crossover Study in Normal Male Volunteers [Study report for protocol C91-255]. Kenilworth (NJ): Schering-Plough Research Institute; 1993 Nov.

4. SCH 961: A Study Evaluating the Pharmacokinetic Profile and Dose Proportionality of Progesterone After Administration of Prometrium® Capsules: A Four-Way Crossover Study in Normal Male Volunteers (NJ): Schering-Plough Research Institute; 1993 Nov.

Figure 1. Patient Distribution (Study No. H89-117).




Abbrevations: MP = micronized progesterone; MPA = medroxyprogesterone acetate; CEE = conjugared equine estrogen

Source: NDA 20,843, Volume 1.7, page 34

Active drugs and placebo were prepared in identical forms. Patients received study medication for a 3 year period. Study medication was packaged in a double-blind fashion using a double-dummy technique. All randomized patients took: 1) an active or placebo CEE tablet each day at bedtime; 2) two active or placebo MP capsules for 12 consecutive days (Days 1-12 in each 28 day cycle at bedtime; and 3) an active or placebo MPA tablet at bedtime. Parameters measured during screening and baseline visits constituted the baseline measurements and included a physical examination, laboratory evaluations, and other measurements. Scheduled visits occurred at 3, 6, 12, 18, 24, 30, and 36 months (see Table 1). Unscheduled visits were conducted as required.

Table 1. Study Procedures (Study No. H89-117).[a]

| | Screening Period (4-6 wks) | | | Baseline Visit | Double-blind Treatment Period[c] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Procedures | V1 | V2 | V3 | Baseline | 6 | 12 | 18 | 24 | 30 | 36 |
| Visit 1 (Initial) Consent Form | X | | | | | | | | | |
| Study Consent Form | | X | | | | | | | | |
| Medical History | X | | | X | | | | | | |
| Demographic Data | X | | | | | | | | | |
| Systolic and Diastolic Blood Pressure | | | X | X | X | X | X | X | X | X |
| Height | | | | X | | X | | X | | X |
| Weight | | | | X | X | X | X | X | X | X |
| Fasting Plasma Glucose | | | | X | | X | | | | X |
| Lipid Panel[b] | | | X | X | X | X | | X | | X |
| Pelvic Examination | | | | X | | X | | X | | X |
| Endometrial Biopsy | | | X | | | X | | X | | X |
| Mammography | | | X | | | X | | X | | X |
| Fasting and 2-hour Postprandial OGTT/Insulin Testing | | | | X | | X | | | | X |
| Fibrinogen | | | | X | | X | | | | X |
| Randomization | | | | X | | | | | | |
| Patient Daily Vaginal Bleeding Assessment Summary | | | | | X—>—>—>—X | | | | | |
| Assess/Record Adverse Events | | | | | X | X | X | X | X | X |
| Record Concomitant Medications | | | | X | X | X | X | X | X | X |

a: Adapted from the May 1989 PEPI Protocol and reflects data made available to SPRI by PEPI.
b: Lipid Panel includes total cholesterol, HDL-C, LDL-C, VLDL-C, and triglycerides.
c: 36 month assessments performed at scheduled 36 month visit or study termination visit.

Source: NDA 20.843, Volume 1.7, page 15

Endometrial tissue was obtained with a Pipelle cannula or with vacuum or suction aspiration or a Novak-type curette. When entry into the uterus was not possible at baseline, these women were not assigned to a study group (18 women were not assigned a study group). When the operator was certain of entry into the uterine cavity but unable to obtain tissue, biopsy results for these women were classified as normal (due to presumed atrophy).

Biopsy slides were reviewed by a local pathologist at each site and followed up by an independent central reader in a blinded manner. Slides with a discrepancy between the local and central reader were reviewed by an arbiter. The result rated for 2 of the 3 evaluators was considered the final result. If there was no agreement between the 3 evaluators, the local rater made the determination as to which evaluation would be the final result (NDA 20,843, volume 1.1, section 3.H. Clinical Data , page 13; and volume 1.7, page 20). Biopsy results were classified as follows (by hierarchy of severity from normal to worst: no hyperplasia, simple (cystic) hyperplasia (least severe), complex (adenomatous) hyperplasia, atypical hyperplasia, and adenocarcinoma (most severe) (NDA 20,843, volume 1.1, section 3.H.Clinical Data, page 13).

As a result of the August 28, 1996 pre-NDA meeting with the Agency, the primary efficacy evaluation was changed to a single evaluation (presence or absence of endometrial hyperplasia) at a single time point (through three years of treatment) for a single pairwise treatment comparison (CEE + MP versus CEE alone). No adjustments to the p values resulting from any of the analyses were made. The proportion of patients with any hyperplasia as the worst diagnosis during the three years of treatment (primary efficacy variable) was analyzed for all evaluable patients (pooled across all centers) and for each pairwise comparison of treatments using Cochran-Mantel-Haenszel test with a chi-square test for homogenicity of results across centers. The time to occurrence of any hyperplasia was analyzed using the Wilcoxon rank sum statistics for the overall treatment group comparison and for each pairwise comparison. Occurrences of adverse events were analyzed by Fisher's exact test.

The mean value, mean change from Baseline, and mean percent change from Baseline were tabulated by analysis interval (i.e., 6, 12, 18, 24, 30, 36 months) and treatment groups (intent-to-treat population) for laboratory values, blood pressure (systolic and diastolic), and body weight. Data for fibrinogen, insulin (both fasting and two hour post-testing), and triglycerides were not normally distributed and a log-transformation was used to facilitate analysis. For LDL-C, a baseline imbalance among the treatment groups existed (p=0.05) and an analysis of covariance using the baseline value as covariate was used.

**4.3 Study population**

A total of 596 women with a uterus (efficacy evaluable population) were randomly assigned to the five treatment regimens. 239 of these patients with a uterus received either CEE + MP or CEE alone (CEE + MP = 120 patients; 119 patients received CEE alone). For the efficacy evaluable population, the average patient age was 56.2 years with 5 years duration of menopause; the majority were White (90.4%, 216/239). Their average body mass index was 25.7 $kg/m^2$. There were no statistically significant differences in these characteristics between groups. The CEE alone group had the greater proportion (43%) of patients discontinuing the study. The population of patients in the Intent-to-Treat population completing the study was similar among all active combination treatment groups and the placebo group.

**4.4 Inclusion and exclusion criteria**

Inclusion criteria

- female volunteers of all races, with or without a uterus or ovaries
- age between 45-64, inclusive, at the first screening visit
- gives written informed consent
- had to, at end of the placebo run in period:
    - agree to continue study participation
    - demonstrate a minimum of 80% compliance with the placebo regimen as assessed through pill counts
    - not develop any spotting or bleeding, unassociated with endometrial biopsies, or other symptoms that would preclude randomization into the study

Exclusion criteria

- last menstrual period was < 1 year or > 10 years ago
- serum follicle stimulating hormone (FSH) concentrations < 40 mIU/ml
- fasting plasma glucose ≥ 140 mg/dl
- plasma LDL-C ≥ 210 mg/dl at either 2 screening visits or averaging ≥ 190 mg/dl
- fasting plasma triglycerides ≥ 500 mg/dl at either of 2 screening visits or averaging ≥ 400 mg/dl
- body mass index ≥ 40 kg/m$^2$
- history of a thromboembolic event associated with estrogen use
- history of breast or endometrial cancer or a mammogram that is positive or suspect for cancer at baseline
- diabetes, if insulin is required
- treated hypertension, if treatment with >2 antihypertensive agents
- myocardial infarction within 6 months prior to Visit 1
- coronary hearth disease requiring antiarrhythmics or digitalis
- congestive heart failure
- history of stroke or transient ischemic attack
- current thyroid disease
- endometrial hyperplasia at baseline
- malignant melanoma
- severe menopausal symptoms
- history of hip fracture not associated with trauma

**4.5 Screening Period**

An informed consent for the study was obtained from each participant prior to the start of screening. A medical history was obtained from all eligible and consenting volunteers. Prior to randomization, a series of physical examinations and laboratory evaluations were performed:

Physical Exam

Blood pressure; body mass index, pelvic examination

Laboratory Evaluation

On all participants: Lipids and lipoproteins; FSH; SMAC; CBC; fasting plasma glucose; ECG; mammography. On subset of participants: PAP test; TSH; endometrial biopsy.

In addition, successful participants complied with a run-in on placebo of 4-6 weeks between screening and baseline; agreed to continue to participate in the study; demonstrated a minimum of 80% compliance with the placebo regimen as assessed through pill counts; and did not develop any spotting or bleeding unassociated with endometrial biopsies or other symptoms that precluded her randomization into the study.

The following parameters were measured during the screening and baseline visits:

Physical Exam

Systolic and diastolic blood pressure; resting heart rate; height; weight; waist/hip ratio; endometrial biopsy

Laboratory Evaluation

Lipid panel; $HDL_2$-C and $HDL_3$-C; apolipoproteins Q-1 and B; fasting, 1 and 2 hour post-load insulin and glucose, bone density; fibrinogen; and , in 3 clinics, Special Studies: additional hemostasis factors; renin substrate; plasma renin activity; aldosterone; post-heparin lipase activity

Other

Quality of life; bleeding diary; exercise questionnaire; assessment of diet; alcohol use, and smoking

**4.6 Treatment period**

Eligible subjects were randomized, using a randomization scheme controlled by the Coordinating Center, in a double-blinded fashion to the 5 arms of the study. The randomization process was stratified within each clinical center by hysterectomy status to ensure an even distribution of women with and without a uterus to all arms within each clinical center. Subjects were followed at 2 month, 6 month and 12 month examinations during the first year

post-randomization and at 6 month intervals thereafter. Table 2 summarizes the primary baseline and follow-up data collected at these scheduled visits.

Table 2 PEPI Participant Follow Up

| Visit | History | Physical Exam | Laboratory | Other |
|---|---|---|---|---|
| Screening and Baseline | yes | Blood Pressure<br>Body Mass Index<br>ECG<br>~~Pelvic Exam~~<br>Waist/Hip Ratio<br>Mammography | Lipid Panel<br>$HDL_2$-C; $HDL_3$-C<br>Apo A-I; Apo B<br>Insulin/OGTT<br>Fibrinogen<br>Bone Densitometry<br>FSH and Estrone<br>Special Studies | Diary<br>Quality of Life<br>Exercise<br>Diet Assessment<br>Smoking/Alcohol |
| 3 Months | yes | Blood Pressure<br>Body Mass Index | | Diary |
| 6 Months | yes | Blood Pressure<br>Body Mass Index | Lipid Panel<br>Apo A-I; Apo B | Diary |
| 12 Months | yes | Blood Pressure<br>Body Mass Index<br>Pelvic Exam<br>Waist/Hip Ratio<br>Mammography | Lipid Panel<br>$HDL_2$-C; $HDL_3$-C<br>Apo A-I; Apo B<br>Insulin/OGTT<br>Fibrinogen<br>Bone Densitometry<br>Estrone<br>Special Studies | Diary<br>Quality of Life<br>Exercise<br>Diet Assessment<br>Smoking/Alcohol |
| 18 Months | yes | Blood Pressure<br>Body Mass Index | | Diary |
| 24 Months | yes | Blood Pressure<br>Body Mass Index<br>Pelvic Exam<br>Waist/Hip Ratio<br>Mammography | Lipid Panel<br>Apo A-I; Apo B<br>Estrone | Diary<br>Exercise<br>Diet Assessment<br>Smoking/Alcohol |
| 30 Months | yes | Blood Pressure<br>Body Mass Index | | Diary |
| 36 Months | yes | Blood Pressure<br>Body Mass Index<br>Pelvic Exam<br>Waist/Hip Ratio<br>Mammography<br>ECG | Lipid Panel<br>$HDL_2$-C; $HDL_3$-C<br>Apo A-I; Apo B<br>Insulin/OGTT<br>Fibrinogen<br>Bone Densitometry<br>Estrone<br>Special Studies | Diary<br>Quality of Life<br>Exercise<br>Diet Assessment<br>Smoking/Alcohol |

Source: NDA 20,843, Volume 1.8, page 480

Scheduled endometrial biopsies were performed at baseline and annually on all subjects with a uterus. Additional biopsies were performed when warranted for women who experienced unexpected bleeding during the trial. Endometrial tissue was obtained with a Pipelle cannula or with vacuum or suction aspiration or a Novak-type curette. When entry into the uterus was not possible at baseline, these women were not assigned to a study group (18 women were not assigned a study group). When the operator was certain of entry into the uterine cavity but unable to obtain tissue, biopsy results for these women were classified as normal (due to presumed atrophy).

Biopsy slides were reviewed by a local pathologist and followed up by an independent central reader. Slides with a discrepancy between the local and the central reader were reviewed by a third pathologist. In most cases, the final diagnosis was based on agreement between two of the three pathologist. When there was disagreement among the three pathologist, the local reader, who had reviewed the participant's clinical course, selected the final diagnosis.

Biopsy results were classified as follows by hierarchy of severity from normal to worst: no hyperplasia, simple (cystic) hyperplasia, complex (adenomatous) hyperplasia, atypical hyperplasia, and adenocarcinoma.[5] The study protocol required cessation of study medication and unmasking of women with biopsy results classified as complex (adenomatous) hyperplasia, atypia, or adenocarcinoma. Women with simple (cystic) hyperplasia were continued on study medications and were not unmasked. Some women underwent a dilatation and curettage (D&C) or a hysterectomy during the follow-up. Seven women had results more serious than the result from the previous biopsy and in these cases the reported diagnosis was based on the findings of these procedures and not the result of the endometrial biopsy.

When vaginal bleeding occurred a consulting gynecologist, not otherwise involved in the PEPI study, was notified. This gynecologist reviewed the bleeding data, obtained from the PEPI Coordinating Center partial information on drug assignment, reviewed this information, and gave a recommendation of whether an unscheduled biopsy should be performed.

4.7 Evaluation criteria

The efficacy analyses of endometrial biopsy data in the PEPI study are based on the efficacy evaluable population which includes all randomized patients with a uterus. All randomized patients, with and without a uterus, comprise the Intent-to-Treat (ITT) population. The primary safety analyses are based on this population.

Patient visits for obtaining endometrial biopsies were scheduled for baseline and annually thereafter. Analysis intervals (12, 24, and 36 months) are relative to the start of treatment designated as Day 1. Analysis intervals for 12 and 24 months were defined as the 12 or 24 month biopsy date plus 6 months post biopsy date. If the 12 month biopsy visit was missing, all biopsy results for that patient were used in the 12 month analysis. If the 24 month biopsy visit was missing then the results for the 12 month analysis was used for the 24 month analysis interval. The 36 month analysis interval included all biopsy results. Results for efficacy evaluable patients with either no follow up biopsy performed but who remained in the study or who had inadequate endometrial tissue from a biopsy were considered to be "normal", which is consistent with the original PEPI analysis.

For the analyses of presence/absence of hyperplasia, the biopsy result considered final is used. If the local and central readers disagreed and an arbiter reading was sought, the result noted for two of the three readings was considered to be the final result. If all three readers disagreed, the local reader determined which of the evaluations would be the final result. Therefore, the results given for each patient over the entire three year treatment period represent the worst biopsy results (primary efficacy endpoint).

5. Hendrickson M, Kempson R. Endometrial hyperplasia. Major problems in pathology. Philadelpia Pa: WB Saunders; 1980;12:285-318.

**Reviewer's Comment**

**The sponsor was requested to provide the definition of the local reader, central reader, and arbiter as concerns the endometrial biopsy final diagnosis. In a letter received from the sponsor January 19, 1998, the following procedure was outlined: "After evaluating the slide themselves, the local reader sent the slide to the central reader. The central reader telephoned the local site with the results. If a discrepancy existed, the local reader instructed the central reader to forward the slide to the umpire (arbiter) for evaluation. The umpire informed the local site of the reading. If the reading was again in disagreement with the other two readings, the local physician made a determination (with no official guidelines to follow) of the final diagnosis.**

4.8 Withdrawals and compliance

The final study completion status of patients in the efficacy evaluable population (i.e., women with a uterus) is presented in Table 3. The proportion of patients completing the study was similar among all active combination treatment groups and the placebo group. The CEE alone group had a greater proportion (55%) of patients discontinue the study.

Table 3 Summary of Final Status: Completion/Discontinuation Data Following Randomization by Treatment Group in the Efficacy Evaluable Population (Study No. H89-117).

| | Number (%) of Patients | | | | | |
|---|---|---|---|---|---|---|
| Status | Total N=596 | MP + CEE N=120 | CEE N=119 | MPA + CEE (Cyclic) N=118 | MPA + CEE (Continuous) N=120 | Placebo N=119 |
| Completed Study[a] | 439 (74) | 95 (79) | 54 (45) | 94 (80) | 101 (84) | 95 (80) |
| Discontinued Study | 157 (26) | 25 (21) | 65 (55) | 24 (20) | 19 (16) | 24 (20) |

a: Completed 36 months on randomized treatment (includes patients with temporary treatment interruptions but not permanent discontinuations prior to 36 months).
Abbreviations: MP = micronized progesterone; MPA = medroxyprogesterone acetate; CEE = conjugated equine estrogen
Data Source: Study H89-117 Clinical Study Report, Attachment 4 and Appendix C-2

Source: NDA 20, 843, Volume 1.1, Section 3.H. Clinical Data, page 36

For the Intent-to-Treat population, the proportion of patients completing the study was also similar among the active combination groups and the placebo group. As in the efficacy evaluable population, the CEE alone group in the Intent-to-Treat population had a greater proportion (43%) of patients discontinuing the study. See Table 4.

The frequency of study medication discontinuation due to adverse events in the MP+CEE group (16%, 29/178 Intent-to-Treat population) was similar to placebo (19%, 33/174) and the other active estrogen-progestin treatment groups (15%, 26/174 for the CEE +cyclic MPA group; 12%, 21/174 for the CEE + continuous MPA group). In the MP+CEE group, the most common adverse events resulting in discontinuation were breast carcinoma (2%, 4/178) and vaginal bleeding (2%, 3/178).

A greater proportion of patients in the CEE alone group (39%, 69/175) discontinued due to adverse events. Adenomatous hyperplasia (12%, 21/175), vaginal bleeding (9%, 15/175), and atypia (5%, 8/175) were the most common adverse events resulting in study medication discontinuation in the Intent-to-Treat population.

Table 4 Summary of Final Status: Completion/Discontinuation Data Following Randomization by Treatment Group in the Intent-to-treat Population (Study No. H89-117).

| Status | Number (%) of Patients | | | | | |
|---|---|---|---|---|---|---|
| | Total N=875 | MP + CEE N=178 | CEE N=175 | MPA + CEE (Cyclic) N=174 | MPA + CEE (Continuous) N=174 | Placebo N=174 |
| Completed Study[a] | 665 (76) | 141 (79) | 100 (57) | 143 (82) | 147 (84) | 134 (77) |
| Discontinued Study | 210 (24) | 37 (21) | 75 (43) | 31 (18) | 27 (16) | 40 (23) |

a: Completed 36 months on randomized treatment (includes patients with temporary treatment interruptions but not permanent discontinuations prior to 36 months).
Abbreviations: MP = micronized progesterone; MPA = medroxyprogesterone acetate; CEE = conjugated equine estrogen
Data Source: Study H89-117 Clinical Study Report, Attachment 4 and Appendix C-2

Source: NDA 20, 843, Volume 1.1, Section 3.H. Clinical Data, page 46

4.9 Efficacy analysis

Primary efficacy analysis

The efficacy results refer to the efficacy evaluable population (596 patients with a uterus). Approximately 120 endometrial biopsies were performed at baseline for each of the study groups. At the end of the 3-year trial, a total of 527 participants (88%) underwent biopsies. Reduction in the number of annual biopsies for all groups were due to loss to follow-up or participants' refusal to have another biopsy. In addition, a total of 174 unscheduled endometrial biopsies were performed. Ten patients (8.4%/119 patients) taking placebo had 11 unscheduled biopsies, while 79 (66.4%/119) patients taking CE-alone had at least one unscheduled biopsy.

A total of 506 women (85%) had normal results for all follow-up biopsies (36 months). Endometrial hyperplasia or endometrial adenocarcinoma was reported for 90 women (15%). In women given CEE-alone, 74 of 119 (62%) developed some type of endometrial hyperplasia and 41 of 119 (34%) had complex hyperplasia or atypia. Women in the CEE-alone group were more likely to develop simple, complex, or atypical hyperplasia as their most abnormal diagnosis than women given placebo.[6] Among the women receiving placebo, one case each of simple hyperplasia (1%), complex hyperplasia (1%), and adenocarcinoma (1%) occurred. Ten cases of simple (cystic) hyperplasia, 2 cases of complex (adenomatous) hyperplasia, and one of atypical hyperplasia were distributed among the three estrogen-progestin groups. The proportion of patients with no hyperplasia or hyprplasia was generally similar among the estrogen-progestin combination and placebo groups. In the MP+CEE group there were five (4.2%) reported cases of simple hyperplasia and one atypia (0.8%). Table 5 summarizes endometrial changes based on the most extreme endometrial biopsy result during the entire three-year treatment period. The number of patients who developed endometrial hyperplasia was statistically significantly lower in the MP+CEE group compared to the CEE-alone group ($p<0.001$).

Endometrial changes based on the most extreme endometrial biopsy result at the 12 month evaluation were qualitatively similar to those observed at the 36 months evaluation, except that fewer patients in all treatment groups had developed endometrial hyperplasia (546 patients showed no hyperplasia (92%) and 50 (8.4%) patients showed hyperplasia at 12 months). At 24 months, 525 patients (88%) showed no hyperplasia and 71 patients (12%) showed hyperplasia. A survival analysis plot of the proportion of patients in the five treatment groups by the time since the

6. The Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen=Progestin Interventions (PEPI) Trial. JAMA 1996;275:370-5.

start of study treatment to any hyperplasia is presented in Figure 2. 'Time' is defined as the number of days since the start of study treatment. The plot illustrates graphically that the proportion of patients with no hyperplasia was significantly greater for the MP+CEE group compared to the CEE-alone group ($p<0.001$), based on the Wilcoxon Rank Sum chi square test).

Table 5 Efficacy Evaluable Population Endometrial Changes: Final Status of Patients Based on Their Most Extreme Results During Three-Year Treatment Period (36 Month Evaluation) (Study No. H89-117)[a]

| | Number (%) of Patients | | | | | |
|---|---|---|---|---|---|---|
| Endometrial Diagnosis[c] | MP + CEE (A) N=120 | CEE (B) N=119 | MPA + CEE (Cyclic) (C) N=118 | MPA + CEE (Continuous) (D) N=120 | -- Placebo (E) N=119 | Overall[b] Treatment p Value |
| NO HYPERPLASIA | 114 (95) | 45 (38) | 112 (95) | 119 (99) | 116 (97) | <0.001 |
| HYPERPLASIA | 6 ( 5) | 74 (62) | 6 ( 5) | 1 ( 1) | 3 ( 3) | |
| Adenocarcinoma | 0 | 0 | 0 | 0 | 1 ( 1) | |
| Atypical hyperplasia | 1 ( 1) | 14 (12) | 0 | 0 | 0 | |
| Complex hyperplasia | 0 | 27 (23) | 2 ( 2) | 0 | 1 ( 1) | |
| Simple hyperplasia | 5 ( 4) | 33 (28) | 4 ( 3) | 1 ( 1) | 1 ( 1) | |

| Pairwise Comparisons (p Value)[b] | | | | |
|---|---|---|---|---|
| Diagnosis | A vs B | A vs E | A vs C | A vs D |
| No Hyperplasia vs Hyperplasia | <0.001 | 0.316 | 0.982 | 0.058 |

Abbreviations: MP = micronized progesterone; MPA = medroxyprogesterone acetate; CEE = conjugated equine estrogen

a: Includes all patients who had at least one biopsy during the 3-year treatment period (final status equals the 36 month status as described in **Section 3.6.1.3.**).

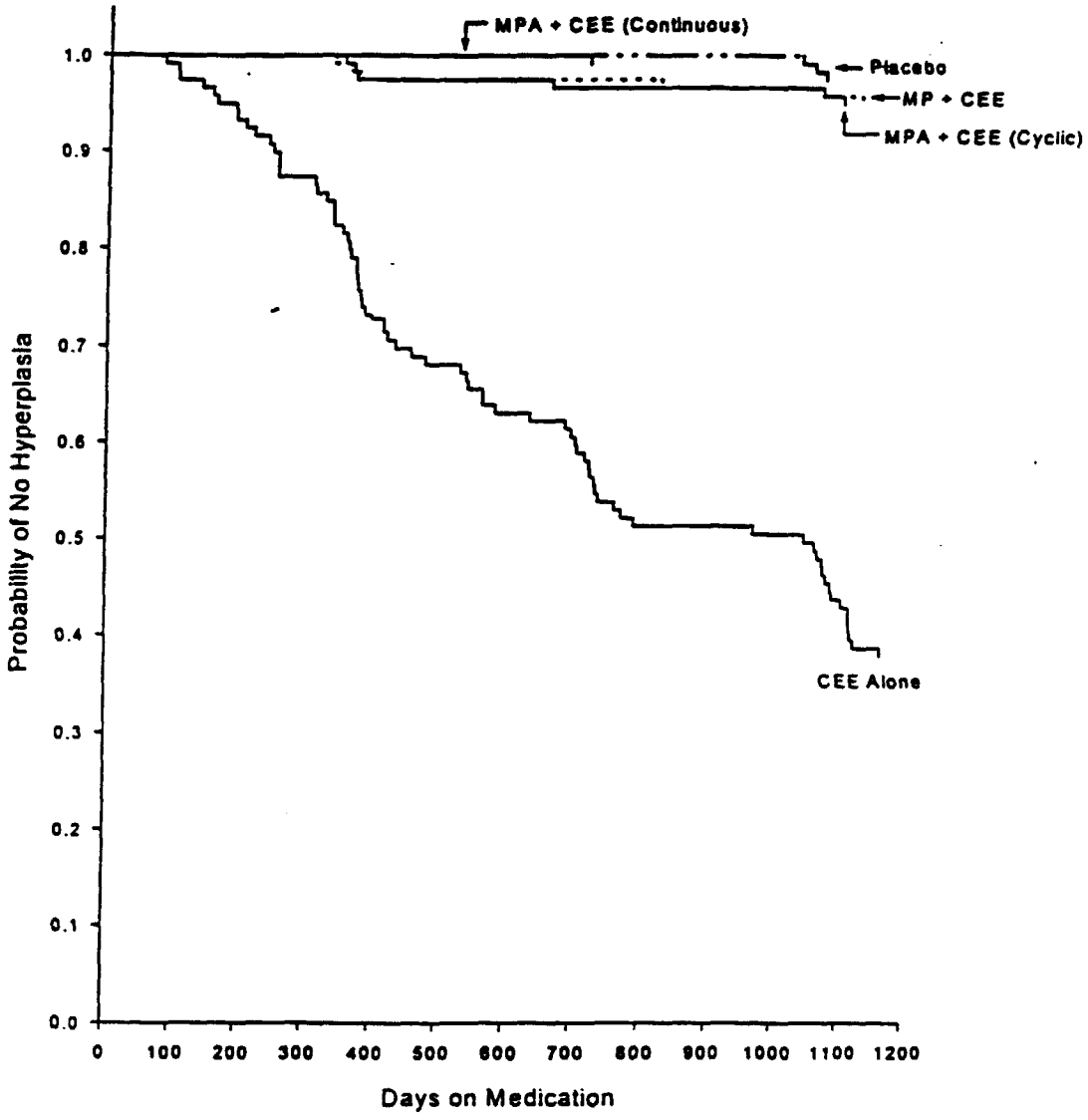
b: Overall p value and pairwise comparisons based on Cochran-Mantel-Haenszel procedure.

c: Hierarchy of endometrial biopsy for hyperplasia range from least to most extreme as follows: no hyperplasia (least extreme), simple hyperplasia, complex hyperplasia, atypical hyperplasia, and adenocarcinoma (most extreme).

Data Source: **Attachment 8 and Appendix C-3**

Source: NDA 20, 843, Volume 1.7, page 39

Figure 2. Survival Plot of Time to Any Hyperplasia for the Efficacy Evaluable Population (Study No. H89-117).




Source: NDA 20,843, Volume 1.7, Page 43

**Reviewer's Comment**

**The process by which endometrial biopsy slides were reviewed and a final diagnosis reached is described herein, section 4.2 Design, namely: 1) evaluation by local pathologist; 2) evaluation by central pathologist; 3) evaluation by arbiter pathologist if 1 and 2 disagree; 4) accept as final diagnosis the results rated for 2 of the 3 pathologists; 5) if disagreement between the 3 pathologists, local pathologist selected the final diagnosis. The February 7, 1996 publication by The Writing Group for the PEPI Trial states that of the 2418 biopsies performed during the PEPI Trial, 164 (6.7%) required the opinion of the arbiter pathologist. In 30 of these cases (1.2%), three different opinions were reported and the diagnoses were assigned by the PEPI gynecologist.[6] Information received from the sponsor, dated January 19, 1998, in response to a FDA request to clarify the procedure used to read the endometrial biopsies in the PEPI Trial, indicates that "The umpire (arbiter) informed the local site of the reading. If the reading was again in disagreement with the other two readings, the local physician made a determination (with no official guidelines to follow) of the final diagnosis."**

**In addition, the January 19, 1998 letter from the sponsor addresses the Agency's concern regarding the final diagnosis for Patient [redacted], Center 1. Per the sponsor "—when the umpire's reading was also different from the local and central readers, a fourth evaluation (at the local site by a different pathologist) was made of the same slide, which resulted in a diagnosis of "proliferative endometrium". The local physician then recorded the final determination to be "normal" based on this finding." This procedure, resulting in a normal diagnosis, was outside the endometrial biopsies guidelines established in the original PEPI protocol (see NDA 20,843, Volume 1.8, Appendix A-1, Study Protocol, page 467).**

**Concerned for the possible impact on the study results due to patient [redacted], the Agency's Statistical Reviewer reanalyzed the PEPI study data with patient [redacted] as having a result of endometrial hyperplasia at the 12-month time point instead of a normal result. The results of this reanalysis do not alter the conclusion that there is a significantly lower incidence of endometrial hyperplasia in the MP+CEE treatment group than in the CEE-only treatment group (CMH; $p<.001$) and there is a significant difference between the survival curves of the MP+CEE group and the CEE-only group (Wilcoxon; $p<.001$). Please see the Statistical Review and Evaluation for additional information.**

4.10 Safety analysis

Study Number H89-117

Deaths

Table 6 lists patients who died during the PEPI Trial. Two patients in the MP+CEE group and one patient in the CEE+MPA (Cyclic) group died:

Patient [redacted] was a 54 year old White female, with a negative family history for breast cancer, who had a hysterectomy in 1968, followed by estrogen use, both orally and by injection from 1971 until entry into the PEPI Trial on December 12, 1990. Left breast mass was confirmed by mammography and ultrasound on December 16, 1991 and patient discontinued study medication on December 19, 1991. Death occurred on November 23, 1993 due to breast carcinoma with lung metastases.

Patient [redacted] was a 59 year old White female, with a positive smoking history, who had a hysterectomy and bilateral oophorectomy in 1980 without mention of post-hysterectomy estrogen replacement therapy prior to entry into the PEPI Trial on September 7, 1990. Primary cholangiocarcinoma was diagnosed by biopsy in August 1991 and patient discontinued study medication on August 12, 1991. Death occurred on November 15, 1992 due to liver cancer.

Patient [redacted] was a 54 year old White female, with a positive smoking history, who had a hysterectomy in

6. The Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. JAMA 1996;275:370-5.

1982, followed by estrogen use for nine years prior to entry into the PEPI Trial on July 1, 1990. Non-small cell lung carcinoma was diagnosed October 1991 and patient discontinued study medication on 10/29/91. Death occurred on February 29, 1992 due to lung cancer.

Table 6 Patient Deaths (Study No. H89-117).

| Patient No. | Center No. | Patient Age (years) | Treatment Group | Adverse Event | Patient Outcome |
|---|---|---|---|---|---|
| | 1 | 52 | MP+CEE | Breast carcinoma, lung metastases | Patient died |
| | 4 | 58 | MP+CEE | Liver cancer | Patient died |
| | 1 | 52 | MPA+CEE (Cyclic) | Lung cancer | Patient died |

Abbreviations: MP = micronized progesterone; MPA = medroxyprogesterone acetate; CEE = conjugated equine estrogen
Data Source: Appendices C-4 and C-5

Source: NDA 20,843, Volume 1.7, page 75

**Major adverse events**

In the PEPI protocol, adverse events were defined as serious and less serious adverse events (experiences) and were combined and referred to as major adverse events. Please see NDA 20-843, volume 1.6, pages 19-20 for the definition of major adverse events as defined by the PEPI Investigators and the Coordinating Center guidelines.

Major adverse events occuring in at least 2% of patients in any treatment groups in the Intent-to-Treat population are presented in Table 7. The proportion of patients with any major adverse event was generally similar among treatment groups (26% to 33%) with the exception of the CEE only group, for which 55% of patients reported at least one major adverse event, due in a large part to the greater incidence of adenomatous hyperplasia, abnormal vaginal bleeding, and atypia. The most common adverse events in the MP+CEE group were breast carcinoma (2%, 4/178), breast excisional biopsy (2%, 3/178), and cholecystectomy (2%, 3/178). There were no significant differences between the MP+CEE group and the MPA+CEE groups (both Cyclic and Continuous MPA), and placebo groups for any major event.

**Non-major adverse events**

The non-major adverse events reported in the PEPI Study at the 6 month treatment visit (collected from a symptom checklist in the Intent-to-Treat population) are representative, in general, of the type and frequency of non-major events reported at subsequent visits. The most common (≥ 5%) adverse events reported in the MP+CEE group, at the 6 month treatment visit were breast tenderness (13%,22/176), headache (7%,13/176), and abdominal bloating (6%, 27/170). In the CEE alone group, the most common adverse events were headache (11%, 19/173), breast tenderness (8%, 14/172), and vaginal discharge (6%, 11/173). Hot flashes were reported more often in the placebo group (16%, 27/170). At the 36 month visit, headache and joint pain (8%, 14/172; 8%, 13/172) were most common adverse events which were similar to the incidence of both events in the placebo group. Breast tenderness was reported in 4% (7/172) of patients in the MP+CEE group. Joint pain was reported in 9% (16/170) in the CEE alone group. The incidence rates of breast tenderness in all active treatment groups in the PEPI Study tended to decrease over time during the three-year treatment period. Hot flashes tended to be consistently reported in the placebo group throughout the 36-month treatment period.

Table 7. Major Adverse Events Reported in At Least 2% of Patients in Any Treatment Group: Intent-to-treat Population (Study No. H89-117).[a]

| Adverse Event | Number (%) of Patients | | | | |
|---|---|---|---|---|---|
| | MP + CEE (A) N=178 | CEE (B) N=175 | MPA + CEE (Cyclic) (C) N=174 | MPA + CEE (Continuous) (D) N=174 | Placebo (E) N=174 |
| Number (%) of Patients with any AE[b] | 56 (31) | 97 (55) | 46 (26) | 58 (33) | 52 (30) |
| Adenomatous hyperplasia | 0 | 28 (16) | 2 (<1) | 0 | 1 (<1) |
| Abnormal vaginal bleeding | 1 (<1) | 18 (10) | 1 (<1) | 1 (<1) | 0 |
| Atypia | 1 (<1) | 14 ( 8) | 0 | 0 | 1 (<1) |
| Severe headache | 1 (<1) | 2 (<1) | 3 ( 2) | 1 (<1) | 5 ( 3) |
| Breast needle biopsy | 1 (<1) | 2 (<1) | 1 (<1) | 5 ( 3) | 0 |
| Cholecystectomy | 3 ( 2) | 1 (<1) | 4 ( 2) | 4 ( 2) | 2 (<1) |
| Breast carcinoma | 4 ( 2) | 1 (<1) | 1 (<1) | 0 | 1 (<1) |
| Abnormal GTT | 0 | 1 (<1) | 1 (<1) | 4 ( 2) | 1 (<1) |
| Abnormal vaginal bleeding, recurrent | 0 | 3 ( 2) | 0 | 0 | 0 |
| Basal cell carcinoma | 2 ( 1) | 3 ( 2) | 0 | 3 ( 2) | 1 (<1) |
| Breast excisional biopsy | 3 ( 2) | 2 ( 1) | 0 | 1 (<1) | 1 (<1) |
| Facial plastic surgery | 1 (<1) | 0 | 0 | 1 (<1) | 3 ( 2) |
| Root canal | 0 | 2 ( 1) | 0 | 3 ( 2) | 1 (<1) |

Abbreviations: MP = micronized progesterone; MPA = medroxyprogesterone acetate; CEE = conjugated equine estrogen

a: Major adverse events were defined as follows: 1) death or any event that was acute, life threatening, or disabling; 2) any hospitalization or outpatient surgical procedure; 3) any medical experience leading to an investigator prescribed discontinuation of study drug 7 or more days; 4) any event anticipated per protocol, without requiring discontinuation of study drug (severe depression, severe headache, newly diagnosed diabetes, symptomatic or active gall bladder disease, abnormal vaginal bleeding); 5) any event anticipated per protocol requiring permanent discontinuation of study drug (deep vein thrombophlebitis, pulmonary embolus, transient ischemic attack (TIA), or amaurosis fugax, adenomatous endometrial hyperplasia, atypical endometrial hyperplasia, endometrial cancer, blood pressure exceeding safety limits, breast cancer, or other estrogen-dependent tumor).

b: Number (percent) of subjects having at least one event, each patient is counted only once.

Data Source: Study H89-117 Clinical Study Report, Attachment 10 and Appendices C-4 and C-5

Source: NDA 20,843, Volume 1.6,vSection 8.H. Integrated Summary of Safety, page 22

**Follow-up for endometrial hyperplasia**

The PEPI Study participants with a diagnosis of simple (cystic) hyperplasia continued to receive their study medications and had an endometrial biopsy within 6 months or at the next scheduled visit, whichever came first.[6] Participants with a diagnosis of complex (adenomatous) or atypical hyperplasia had their study medications permanently discontinued and elected to either: 1) receive from the PEPI gynecologist an 8-month course of 10 mg/day of MPA to reverse the hyperplasia, followed by an endometrial biopsy to assess the effect of therapy; 2) seek care elsewhere at her own expense; or 3) choose an alternate course of therapy with the PEPI gynecologist.

Participants permanently discontinued were followed up for the remainder of the study by the PEPI investigators. The participant with adenocarcinoma had her study medication permanently discontinued, was referred to a gynecologist for individual management, and was followed up for the remainder of the study.

**Laboratory Test Results**

**Plasma Lipid Profiles**

Mean Baseline, mean change, and mean percent change from Baseline for plasma lipid profiles were calculated. Each active treatment group was associated with a significantly greater increment in mean HDL-C levels than placebo (Bonferroni $p<.001$). The average increases in HDL-C levels in the Intent-to-Treat population were similar in women assigned to CEE alone or MP+CEE, and these women had sifnificantly greater HDL-C elevations (Bonferroni $p<.004$) than women assigned to CEE with cyclic or continuous MPA.[7] HDL-C levels increased during the first 6 to 12 months, for all hormone regimens, and gradually decreased thereafter, although not to the baseline level.

The mean change from Baseline in LDL-C and triglycerides (LDL-C decreased and triglycerides increased) was similar across the active treatment groups. The MP+CEE group was significantly different compared to the placebo group ($p<0.01$) at all post-Baseline time points. Plasma lipid profile analysis for the efficacy evaluable population were generally consistent with the Intent-to-Treat population analysis (NDA 20-843, Volume 1.7, page 55).

**Fibrinogen**

Changes in Fibrinogen levels varied significantly by treatment assignment (Bonferroni $p<.001$). In pairwise comparisons, women assigned to placebo had greater increases in fibrinogen than women assigned to active treatment groups which showed no significant differences between treatment groups.[7]

**Glucose and insulin**

Mean change in 2-hour insulin (primary outcome measure for carbohydrate metabolism) did not differ significantly by treatment assignment. Fasting insulin levels decreased slightly but not significantly in women assigned to active treatments. Two-hour glucose levels increased significantly in women assigned to active treatment compared with placebo ($p=.01$). Fasting glucose levels decreased slightly and significantly in all active treatment arms compared to placebo ($p=.03$).[7]

**Blood pressure**

Blood pressure remained stable throughout the evaluation period in all treatment groups, with no significant differences from Baseline or between groups (NDA 20-843, Volume 1.7, page 61).

**Study Number C90-557**

This was a randomized, double-blind, placebo-controlled, multicenter, parallel-group dose-response study evaluating the progestational activity (endometrial secretory transformation) of micronized progesterone (SCH 961) in 124 estrogen-primed postmenopausal women. Estrogen-priming was accomplished with CEE 0.625 mg/day for 6 weeks (cycle 1 and Days 1-15 of Cycle 2). SCH 961 doses of 100 mg (N=26), 200 mg (N=26), 300 mg (N=23), and 400 mg (N=25) QD versus placebo (N=24) were administered for 10 days per cycle with daily Premarin® for 3 cycles (Cycles 2-4). An endometrial biopsy was performed on Day 6 of Cycle 2 and again on Day 26 of Cycle 4.

The sponsor's efficacy evaluable population consisted of 107 patients who completed 3 cycles of double-blind treatment and who had evaluable endometrial biopsies. "Of the four doses studied, only the 400 mg/day dose produced a significantly greater proportion ($p<0.001$) of complete secretory activity in the subjects than did placebo." (See Medical Officers Review of NDA 19,781).

7. The Writing Group for the PEPI Trial. Effects of estrogens/progestins regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. JAMA 1995;273:199-208.

There were no patient deaths in the C90-577 study (NDA 20-843, Volume 1.1, Section 3.H. Clinical Data, page 68). Angina in a 66-year old White female was the one report of a serious adverse event. Of the five patients who discontinued treatment, four discontinued due to mild to severe dizziness and one patient discontinued due to mild dysmenorrhea and moderate irritability. No placebo patient discontinued prematurely due to adverse events. Few significant changes from Baseline were seen in routine laboratory parameters at the end of therapy; none were considered clinically significant.

**Study Number T91-023 (Vargyas Study)**
This study was a single-center, randomized, open-label, parallel group study to evaluate the effects of estrogen/progesterone therapy on the endometrium of 25 postmenopausal women. Eligible patients were randomized to receive Premarin® 0.625 mg (N=12) or 1.25 mg (N=13) daily in combination with SCH 961 200 mg QD for 12 -14 days per cycle for 6 cycles. Endometrial biopsies were performed pre-treatment and during Cycle 6.

"Evaluation of the biopsy specimens taken from postmenopausal women after 6 months of sequential estrogen replacement therapy plus cyclical administration of Utrogestan (micronized progestrone) revealed no evidence of endometrial hyperplasia or carcinoma." (NDA 20-843, Volume 1.1, Section 3.H. Clinical Data, page 30).

There were no deaths in the T91-023 study. Three patient discontinued treatment because of adverse events; one for prolonged vaginal bleeding (receiving SCH 961/Premarin 0.625 mg) and two for weight gain (one for each Premarin® dose group). One patient in the SCH 961/Premarin® 1.25 mg group was lost to follow up.

**4.11 Summary of DSI audit**
A DSI audit has recently been completed. No report is available at this time.

**5. Labeling Review**
A labeling meeting was held on January 13, 1998 to review the proposed labeling for Prometrium. Please see Attachment 3 for the meeting minutes and the required labeling changes.

**6. Reviewer's Assessment of safety and efficacy**
This NDA 20,843 presents information in support of the safety and efficacy of micronized progesterone (MP) in combination with conjugated equine estrogen (CEE) for the prevention of endometrial hyperplasia in women with a uterus. Data from the NIH-sponsored Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, a large prospective, randomized, double-blind, placebo-controlled, multicenter study of 875 postmenopausal women (596 with a uterus), was analyzed by the Schering-Plough Research Institute. The primary efficacy endpoint was the worst endometrial histology assessment based on the endometrial biopsies in women with an intact uterus over the three year treatment period. The comparison of MP+CEE versus CEE alone was identified as the primary efficacy comparison.

Estrogen replacement therapy has been shown to be effective in the management and treatment of moderate to severe vasomotor symptoms associated with the menopause, atrophic vaginitis, and osteoporosis prevention. Despite these benefits, however, unopposed estrogen therapy in women with an intact uterus increases the risk of endometrial hyperplasia, a possible precursor of endometrial adenocarcinoma. The addition of a progestin to estrogen replacement therapy for at least 10 days per cycle effectively reduces the risk of endometrial hyperplasia and subsequently endometrial cancer.

MP+CEE was effective in the prevention of endometrial hyperplasia in women with a uterus. The number of patients who developed any endometrial hyperplasia by the 36 month time point was statistically significantly lower in the MP+CEE group compared to the CEE alone group, 5% compared to 62.2% based on the final 36 month analysis. Qualitatively similar results were observed at the 12 and 24 month time points, 2.5% compared to 36.1% at 12 months and 3.3% compared to 50.4% at 24 months (see Statistical Review and Evaluation).

The frequencies of most major adverse events were similar among treatment groups (26% to 33%) with the

exception of the CEE alone treatment group for which 55% of patients reported at least one major adverse event. This 55% rate is due in large part to the higher incidence of endometrial hyperplasia and abnormal vaginal bleeding in the CEE alone group. The most common major adverse event in the MP+CEE Intent-to-Treat population was breast carcinoma (2%, 4/178), breast excisional biopsy (2%, 3/178) and cholecystectomy (2%, 3/178). Two of the three deaths in the study occurred in the MP+CEE group; one breast cancer with lung metastasis and one liver cancer. While there was no significant difference between the three combination and placebo groups for any major adverse events, four of the seven breast carcinomas occurred in the MP+CEE treatment group. The impact of exogenous hormones on the risk of breast cancer has been the focus of considerable interest in recent years as the use of exogenous hormones has increased. Many cohort and case-controlled studies in women using hormone replacement therapy have been conducted. Overall, these analyses suggest that the risk of developing breast cancer with hormone replacement therapy use may not increase with short-term use (less than 5 years). With long term use, greater than 10 years, there may be a slightly increased risk of developing breast cancer but other biological factors (i.e., family history, diet, smoking, etc.) must be considered. Since the issue of breast cancer and hormone replacement therapy continues to be an area of intensive ongoing investigation, careful post-marketing surveillance of breast cancer and other major adverse events is warrented.

Of the four cardiovascular risk factors observed (HDL-C, plasma insulin, fibrinogen, and systolic blood pressure), MP+CEE was the only hormone replacement therapy regimen which was found to be statistically similar to CEE alone on its effect on HDL-C. As expected, HDL-C increased to the greatest extent from baseline in the CEE alone group, followed next in magnitude by the MP+CEE group. The mean change in HDL-C from baseline was significantly higher for the MP+CEE group at 12, 24, and 36 months compared to the other combination and placebo groups. There were no significant differences between active treatment groups in regards to plasma insulin, fibrinogen, or systolic blood pressure.

7. Recommended regulatory action

This NDA is recommended for approval. The previously noted labeling changes are being communicated to the sponsor by letter.

/S/

agree /S/ 2/25/98

Theresa H. van der Vlugt, M.D., M.P.H.
Medical Officer, DRUDP

Attachments: Attachment 1: Regulatory History, IND
Attachment 2: Regulatory History, NDA 20,843
Attachment 3: January 13, 1998 Labeling Meeting Minutes and Required Labeling Changes

cc: NDA 20,843 Division File
HFD-580/DMoore/LRarick/TvanderVlugt

**Attachment 1. Regulatory History, IND**

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commercial

information

**Attachment 2. Regulatory History, NDA 20,843**

Status date: January 29, 1998

**NDA 20,843**

| | |
|---|---|
| Name of Drug: | Prometrium®, (Progesterone, USP) |
| Chemical Name: | Pregn-4-ene-3, 20 dione |
| Dosage Form: | 100 mg soft gelatin capsule |
| Date of Submission: | March 10, 1997 |
| Date of Receipt: | March 12, 1997 |
| Date Assigned: | March 21, 1997 |

**Regulatory History**

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| March 12, 1997 | Received from sponsor original new drug application for Prometrium 100 mg capsules to be administered orally for use in the prevention of endometrial hyperplasia in non-hysterectomized post-menopausal women who are receiving conjugated estrogen tablets |
| May 5, 1997 | Memorandum to File regarding the DSI site visits: per medical officer a review of information failed to identify any center(s) that stand out in regards to low or high rates of loss to follow-up or adverse events; no strong preference as to which center(s) to recommend for inspection |
| June 23, 1997 | Telecon Minutes on May 7, 1997 with sponsor to discuss the need for the investigator information from the PEPI trial to be forwarded to the FDA since audit sites cannot be determined from the data submitted; Decisions Reached: Schering should send details of why they could not get pertinent data; the text portion of the study report should be submitted to the IND for review; ACTION ITEMS: MO to develop checklist of important items to be analyzed in the audit |
| July 17, 1997 | Four-Month Safety Update Report for Prometrium containing information on three Phase IV post-marketing clinical studies conducted in Canada:<br>Study 095-926<br>randomized study comparing the quality of life, pharmacoeconomics and safety of Prometrium to Provera in combination with Premarin in PMW; 250 patients randomized; 183 patients collected and analyzed, 22 patients terminated due to adverse events (8 in Prometrium, 14 in Provera)<br>Study 095-947: randomized, open study comparing the effects of Prometrium 200 mg and Provera 5 mg in combination with Premarin on nocturnal sleep and day time vigilance in PMW; 21 patients completed study; 2 patients discontinued ( one with edema, paresthesia in arms and legs, mental confusion, one with weight gain and edema in legs and hands<br>Study 095-948: randomized, open study comparing effects on brachial artery vasodilatory capacity in PMW; 29 patients; analysis of data in progress; 3 patients discontinues (one with visual migraines, one with severe rash, one with abdominal pain and bloating<br>Post marketing experiences from Besins-Iscovesco Pharm: 85 events collected from France, Belgium and Switzerland and Netherlands (15 assessed as serious); liver toxicity = 5 (possibly related); meningitis = 1 |

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| | (assessed as unrelated);hemiplegia =1 (unrelated);fetal deaths = 3; endometrial hyperplasia = 1; pulmonary embolism = 1; adenocarcinoma of pancreas = 1 (death); increase urine acetone =1; allergic reaction = 1<br>Post-Marketing Experiences from Schering-Plough Canada: 203 adverse experiences: severe somnolence = 1 (related); severe bloating = 1 (related); severe exudative rash = 1 (probably related); severe intermenstrual bleeding = 1; depression = 1 (unrelated); severe allergic reaction = 2; fetal disorders = (unrelated); mammary epithelioma = 1 (unrelated) |
| August 11, 1997 | Memorandum to File: per medical officer the following list of questions regarding endometrial biopsy procedures should be submitted to DSI for investigation during site inspection visit:<br>Per PEPI Protocol:<br>1) Were screening endometrial biopsies completed for all participants per schedule?<br>2) Were annual endometrial biopsies performed per protocol?<br>3) Following local endometrial slide evaluation, were slides consistently sent for reading at the central laboratory?<br>4) When the local and the central pathologists agreed on the diagnosis of endometrial hyperplasia was this final diagnosis appropriately recorded in the CRF and communicated to the participant?<br>5) If there was a discrepancy between both of the primary pathologist, was an arbiter third pathologist consulted? Was the final diagnosis adjudicated? |
| Sept. 22, 1997 | Internal Meeting Minutes to discuss the status of NDA; discussion points: audit site selection to be discussed with Dr. Turner, no sites appear outstanding; current medical, biopharm, and chemistry reviews are pending; the sponsor will request a categorical exclusion for the EA; phamacology is complete and approved; goal date for NDA is March 12, 1998; meeting to discuss statistical review will be set up. |
| Sept. 23, 1997 | Sept. 11, 1997 Meeting Minutes: decisions Reached: statistician will develop two scenarios to compare data from evaluable patients with biopsies and patients without biopsies, produce a table listing 12- and 24 month biopsy data on a survival chart as a secondary efficacy variable; heart disease variable will not be considered as primary or secondary variable; any unusual findings in the distribution of dropouts will be noted by the statistician and conveyed to the medical officer. |
| Dec. 2, 1997 | November 12, 1997 Meeting Minutes; to discuss the current status of NDA; Decisions reached: the sponsor should clarify the discrepant pathology reading decisions; the sponsor should provide a time line for the drug interaction study; the time frame for the DSI audit should be determined; the user fee goal date could be extended three months or missing drug-drug interaction study could result in an approvable result of the interaction study required for approval. |
| Dec. 18, 1997 | Meeting Minutes, same date: DSI audit has not been |

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|---|---|
| | scheduled; medical, biometrics, and clinical pharmacology reviews are pending; chemistry and pharmacology reviews are complete; Decisions Reached: of the results of the drug-drug interaction study are submitted within 3 months of the user fee goal date there will be a 3-month extension of the goal date; if results are not submitted the sponsor risks a not-approval action. |
| Jan. 19, 1998 | Response to FDA Request: sponsor request Environmental Assessment categorical exclusion since the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion; sponsor provides information as concerns the endometrial biopsy final diagnosis: local reader evaluates slide and then sends slide to central reader; central reader reaches diagnosis and telephones local reader with results; if a discrepancy existed the local reader sent slide to arbiter; arbiter reads slide and informs local site of reading; if reading in disagreement with the other two readings, the local reader makes a determination (with no official guidelines) of the final diagnosis; regarding patient 12, center 1 all three readings differed and a 4th reader(different pathologist at local site)gave diagnosis of "proliferative endometrium"; local reader recorded final diagnosis as "normal" |

**Attachment 3. January 13, 1998 Labeling Meeting Minutes and Required Labeling Changes**

# MEETING MINUTES

**Date:** January 13, 1998 **Time:** 10:30 - 11:30 PM **Location:** Parklawn; Rm 17B43

**NDA:** 20-843 **Drug Name:** Prometrium (progesterone) Capsule

**External Participant:** none

**Type of Meeting:** Labeling

**Meeting Chair:** Dr. Lisa Rarick

**Meeting Recorder:** Mrs. Diane Moore

**FDA Attendees:**

Heidi Jolson, M.D., M.P.H. - Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D. - Medical Officer, DRUDP (HFD-580)
Lana L. Pauls, M.P.H. - Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Sam Haidar, R.Ph., Ph.D. - Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, DB II @ DRUDP (HFD-580)
Lisa Stockbridge, Ph.D. - Regulatory Reviewer, Division of Drug Marketing and Communication (DDMAC; HFD-40)

**Meeting Objective:**

To discuss the Prometrium (NDA 20-843) label for the endometrial protection indication.

**Discussion Points:**

- General
  - the sponsor has reorganized the sections in the label for the secondary amenorrhea indication as requested in the AE letter to NDA 19-781
  - it should be possible to combine the labels from the NDA with the secondary amenorrhea indication and this NDA
- Chemistry
  - **HOW SUPPLIED** section needs to be modified; they have corrected the structure, but the other two comments from the approvable letter for NDA 19-781 still apply
  - the sponsor has not submitted a categorical exclusion for the environmental assessment (EA); FDA will prepare a FONSI

- **ADVERSE REACTIONS** section
  - a title heading that reads, ' _ should be inserted before the first paragraph
  - Table 1 and Table 2 should be combined
  - a table should be proposed of all adverse events greater than 2% including the conjugated estrogens Premarin alone arm to replace table 1
  - the second and third paragraphs that begin, should be deleted
  - the subheadings for Prevention of Endometrial Hyperplasia and Secondary Amenorrhea should be maintained in this section as in the Physician's Package Insert
  - the title, ' should be inserted before the fourth paragraph that begins, The tables should be renumbered so that this table would be Table 4
  - in the title in Table 2, the phrase, should be revised to read, ; the column entitled, should be deleted from the table
  - the fifth paragraph that begins, should be deleted
- **OVERDOSAGE** section
  - this section should be revised so that the first sentence that reads, remains and the rest of the paragraph is deleted
- **DOSAGE AND ADMINISTRATION** section
  - the sponsor should justify the evening dose
- **HOW SUPPLIED** section
  - in the first sentence that begins, should be inserted after '
  - the phrase

Patient Insert

- the Patient Insert should be revised to concur with the Physician description of Information for the Patient
- the warning concerning peanuts should be inserted into the PATIENT INSERT

**Action Items:**

| Item: | Responsible Person: | Due Date: |
|---|---|---|
| • request status on waiver for the categorical exclusion for EA | Mrs. Moore | one week |
| • check on the patient populations in the previous Biopharmaceutics review and Pharmacology section | Dr. Haidar | one week |

**Action Items:**

| Item: | Responsible Person: | Due Date: |
|---|---|---|
| • check first and second paragraphs with comments in FDA AE letter to NDA 19-781 for rates of withdrawal bleeding, etc. | Dr. van der Vlugt | one week |
| • propose a new paragraph to replace | Ms. Meaker | one week |

| | | | |
|---|---|---|---|
| | second paragraph under Clinical Studies section of labeling | | |
| • | check the phrase ' in the third sentence that begins, in the HOW SUPPLIED section with Chemist | Mrs. Moore | one week |

Signature, minutes preparer

Concurrence, Chair

**Post meeting Addendum:**
The paragraphs corresponding with FDA comments in AE letter to NDA 19-781 for rates of withdrawal bleeding are correct per Dr. van der Vlugt.
The terms are proper chemistry descriptions for the conditions in the HOW SUPPLIED section of the labeling per Dr. Rhee.

drafted: dm/1.18.98/n20843sm.113

cc:
NDA Arch:
HFD-580/LRarick/Deputy Director/Tvan der Vlugt
HFD-580/DMoore/SHaidar/ADorantes/KMeaker/LKammerman/LPauls
HFD-580/JMercier

Concurrence:
LPauls, AMitra 01.23.98/KMeaker 01.26.98/Tvan der Vlugt, LStockbridge 01.27.98
HJolson 01.28.98/SSlaughter 01.29.98

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