CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 11839/S68

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 11-839/S-068

Pharmacia & Upjohn
Attention: Donald R. Gieseker, Pharm. D.
Associate Director, Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001-0199

AUG 04 1998

Dear Dr. Gieseker:

Please refer to your supplemental new drug application dated July 31, 1997, received August 4, 1997, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Provera (medroxyprogesterone acetate) 5mg and 10mg tablets.

We acknowledge receipt of your submissions dated September 2, 1997, and January 8, June 29, July 22 and August 3, 1998. The user fee goal date for this application is August 4, 1998.

This supplemental new drug application provides for the use of Provera® for the reduction of endometrial hyperplasia in postmenopausal women receiving 0.625mg conjugated estrogens for 12 to 14 consecutive days per month, either beginning on the 1st day of the cycle or the 16th day of the cycle.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert and container and carton labels dated August 3, 1998). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 11-839/S-068." Approval of this submission by FDA is not required before the labeling is used.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose

to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Healthcare Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact John C. Markow, Project Manager, at (301) 827-4260.

Sincerely,

/S/ 8/4/97

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 11839/S68

MEDICAL REVIEW(S)

NDA 11-839/S-068

Date NDA Submitted:	**7/31/97**
Date NDA Received:	**8/4/97**
Date NDA Assigned:	
Review Completed:	**7/6/98**
Revisions Completed:	**7/29/98**

Medical Officer's Review
(Original Review)

Sponsor: **Pharmacia & Upjohn**

Drug:

Generic: **Medroxyprogesterone Acetate Tablets, USP**
Trade: **Provera® Tablets**
Chemical: **Pregn-4-ene-3,20-dione,, 17-(acetyl-loxy)-6-methyl-,(6α)-**

Route: **Oral**

Dosage Form: **Tablet**

Strength: **5 mg**
10 mg

Proposed Indication: **Reduce the incidence of endometrial hyperplasia and endometrial carcinoma in nonhysterectomized postmenopausal women.**

Related Submission: **NDA 11-839/S-068, Amendment 001 dated: 1/8/98**

Related Documents: ***Minutes of Meetings*** **dated: 8/8/97**
Minutes of Teleconference **dated: 8/16/98**

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1. Resume

In support of the use of Provera ® (medroxyprogesterone acetate tablets [MPA]) for 12-14 days each month in combination with continuous estrogen replacement for the prevention of estrogen induced endometrial hyperplasia and endometrial carcinoma in nonhysterectomized post-menopausal women, the sponsor has submitted the results of two published adequate and well-controlled trials: 1) a pivotal Phase III clinical trial, the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial which was sponsored by the National Institutes of Health under a research project cooperative agreement (IND and 2) a supportive prospective 1-year, double-blind, randomized, multicenter study, The Menopause Study Group conducted at 99 sites in the United States and Europe by The submission also includes other supportive publications on the prevention of estrogen induced endometrial hyperplasia and carcinoma by progestins, the effect of combined estrogen and progestin therapy on cardiovascular risk factors, bone mineral density, and the risk of breast cancer. At the September 16, 1997 teleconference with the Division, the sponsor was asked to provide feedback to the Division on a labeling issue (the use of Provera® with "estrogen replacement therapy" instead of Provera® with Premarin® which was used in both studies), and to verify that the wet-granulation process will be used instead of direct compression during manufacturing of the drug product. The sponsor verified that the wet-granulation process will be used and that they have no immediate plans to change the process. Amendment 001 to NDA 11-839/S-068 was submitted on January 8, 1998 in response to the Division's request for information on the labeling issue.

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 (conjugated equine estrogen [CEE] plus cyclic MPA, CEE plus continuous MPA, and CEE plus cyclic micronized progesterone [MP]) were reviewed and reported upon). Trial results provided adequate evidence that combining CEE with cyclic or continuous MPA, or cyclic MP, protected the endometrium from hyperplastic changes associated with estrogen-only therapy.

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

The Menopause Study Group Trial was a double-blind, randomized, placebo-controlled, multicenter study with one year of treatment in 1,724 postmenopausal women with a uterus. Four combinations

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[1] Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. JAMA 1995a;275:370-5.

[2] Woodruff JD, Pickar JH. Incidence of endometrial hyperplasia in postmenopausal women taking conjugated estrogens (Premarin) with medroxyprogesterone acetate or conjugated estrogens alone (The Menopause Study Group). Am J Obstet Gynecol 1994;170:1213-23.

of conjugated estrogens (Premarin®) and MPA (CEE was given continuously, MPA was given cyclically or continuously) were evaluated in preventing endometrial hyperplasia. Study results provided adequate evidence that combining cyclic or continuous MPA with Premarin® protects the endometrium from hyperplastic changes associated with estrogen-only therapy.

In the Menopause Study Group Trial, endometrial biopsies were performed at baseline and during days 22 to 28 of cycles 6 and 13. Terminology used to report endometrial hyperplasia was as follows: cystic or adenomatous hyperplasia without atypia or cystic or adenomatous hyperplasia with atypia. This terminology corresponds to the classification of simple hyperplasia, complex hyperplasia; simple atypical or complex atypical hyperplasia, respectively. Only one pathologist evaluated all endometrial biopsy specimens. The incidence of endometrial hyperplasia did not differ significantly between any of the conjugated estrogens/MPA regimens and was significantly lower in the combination groups than in women treated with conjugated estrogens alone.

Provera® Tablets are currently indicated for the treatment of secondary amenorrhea and abnormal uterine bleeding due to hormone imbalance in the absence of organic pathology, such as fibroids or uterine cancer. Each Provera® tablet for oral administration contains 2.5 mg, 5 mg, or 10 mg of medroxyprogesterone acetate.

2. Background

2.1 Regulatory history

Compressed Tablet Provera® was first marketed in strengths of 2.5 and 10 mg in early 1960 by The Upjohn Company. In September 1996, Pharmacia and Upjohn assumed the sponsorship of Provera®. Pharmacia and Upjohn currently market Provera® 2.5, 5, and 10 mg tablets for the treatment of secondary amenorrhea and abnormal uterine bleeding due to hormone imbalance in the absence of organic pathology, such as fibroids or uterine cancer.

On July 31, 1997, the sponsor resubmitted the current efficacy supplement (S-068) to the NDA with the proposed indication to reduce the incidence of endometrial hyperplasia and endometrial carcinoma in nonhysterectomized postmenopausal women. A more complete regulatory history extracted from the Division File for NDA 11-839 can be found in Attachment 1.

2.2 Clinical implications of preclinical sections

2.2.1 Chemistry, Manufacturing and Control

Please refer to Chemistry, Manufacturing and Control Review

Medroxyprogesterone acetate is a derivative of progesterone. It is a white-to-offwhite, odorless crystalline powder, stable in air, and melting between 200 and 210°C. It is freely soluble in chloroform, soluble in acetone and in dioxane, sparingly soluble in alcohol and in methanol, slightly soluble in ether, and insoluble in water.[3]

2.2.2 Pharmacology/toxicology
Please refer to Pharmacology review.

The results of a two-year dietary oncogenicity study of medroxyprogesterone acetate in female rats demonstrated a dose-related increased incidence of pancreatic islet hyperplasia and tumors (adenomas and carcinomas) seen at dosages up to 5000 *ug*/kg/day (50 times higher than the level observed in women taking 10 mg of MPA). However, 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. In addition, when MPA is combined with estrogen, as will be done in women with intact uteri, more progesterone receptors are produced and more receptors are available to bind MPA and in its absence more MPA is available to bind to glucocorticoid receptors.

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.[4] 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.[4]

2.3 Human pharmacokinetics/bioavailability
Please refer to the Clinical Pharmacology and Biopharmaceutics Review.

This supplement does not include any clinical pharmacology and biopharmaceutic data.

3. Description of clinical data sources
This application includes the published literature for two clinical trials: 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; and the Menopause Study Group (MSG) Trial: a 12 month, prospective, randomized, double-blind, placebo-controlled multicenter study in 1724 postmenopausal women with a uterus assigned to one of five blinded therapies.

4. PEPI Trial
4.1 Objectives/rationale
Estrogen therapy has been used by substantial numbers of postmenopausal women for relief of menopausal symptoms for over 50 years and, more recently, to prevent bone loss and fracture. However, it has been known since the mid-1970s that unopposed estrogen use may increase the incidence of uterine hyperplasia and cancer. Since the early 1990s, combined estrogen-progestin therapy has become more common as this regimen relieves menopausal symptoms, delays bone loss, and reduces the risk of estrogen-alone induced endometrial hyperplasia and carcinoma.

The primary objectives of the PEPI trial was to assess, among postmenopausal women, pairwise treatment differences in cardiovascular disease risk factors over a 3-year period of treatment between placebo, unopposed estrogen, and three combined estrogen-progestin regimens. The effects of these treatments on

[3] Physicians' Desk Reference. 1998. page 2287.
[4] Williams CL and Stancel GM (1996). Estrogens and progestins. In: Hardman JG, Limbird LE (eds. In chief), Molonoff 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.

cardiovascular risk were likely to be multifactorial. Therefore, four different biological/metabolic systems, which were thought to be affected by estrogen use and believed to influence cardiovascular risk in women, were studied: lipid metabolism, blood pressure, carbohydrate metabolism and coagulation/hemostasis.[5] Other risk factors, not selected as primary endpoints (including endometrial histology at baseline and months 12, 24, and 36), were included in PEPI as secondary endpoints. Nonetheless, it is these secondary endpoints that are the focus of this NDA review.

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.

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 two pills at bedtime (one of CEE or matching placebo and one of MPA or matching placebo) daily and two capsules at bedtime (each with 100 mg of micronized progesterone or matching placebo) for the first 12 days of each cycle (see Table 1). 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. Unscheduled visits were conducted as required.

Table 1 PEPI Treatment Regimens*

Treatment Regimen	Estrogen	Progestin
Arm 1	Premarin @ 0.625 mg daily	Placebo
Arm 2	Premarin @ 0.625 mg daily	Provera @ 10 mg days 1-12; Placebo days 13-28
Arm 3	Premarin @ 0.625 mg daily	Provera @ 2.5 mg daily
Arm 4	Premarin @ 0.625 mg daily	Micronized progesterone @ 200 mg days 1-12
Arm 5	Placebo	Placebo

* Cycles are 28 days in length.

Source: NDA 11-839/S-068, Volume 70.1, page 93

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 (n = 18) or were discontinued if this occurred at a follow-up visit (n = 14). When the operator was certain of entry into the uterine cavity but unable to obtain tissue, biopsy results 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. An arbiter reviewed slides with a discrepancy between the local and central reader. 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 11-839, volume 70.1, page 124). Biopsy results were classified by hierarchy of severity from normal to worst as: no hyperplasia, simple (cystic) hyperplasia, complex (adenomatous) hyperplasia, atypical hyperplasia, and adenocarcinoma (NDA 11-839S-068, volume 70.1, page 124). In 30 cases (1.2%), three different opinions were reported by the three pathologists and the PEPI gynecologist assigned the final diagnoses based on clinical and pathologic information combined.

[5] Writing Group for the PEPI Trial. The postmenopausal estrogen/progestin interventions (PEPI) trial: rationale, design and conduct (I). J Controlled Clin. Trials. 1995a;16(supp):3S-19S.

Women with a biopsy result of simple hyperplasia continued to receive their study medication with a repeat biopsy in 6 months or at the next scheduled visit. Women with biopsy results classified as complex or atypical hyperplasia or cancer were unmasked, had their study medication discontinued, and were offered treatment by the PEPI gynecologist or elsewhere.

4.3 Study population

A total of 596 women with a uterus were randomly assigned to the five treatment regimens. 238 of these patients with a uterus received either CEE alone or placebo (119 patients each arm); 120 patients received CEE + MP; and 238 received CEE + MPA (118 received CEE + cyclic MPA and 120 received CEE + continuous MPA). The average patient age was 56.2 years with 5 years duration of menopause; 91% were Caucasian. 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 greatest 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 (NDA 11-839/S-068, Volume 70.1, Pages 91 and 123)

female volunteers of all races, with or without a uterus
age between 45-64, inclusive, at the first screening visit
cessation of menses at least 1 year but not more than 10 years prior to enrollment
follicle-stimulating hormone level of at least 40 mIU/mL
normal or atrophic endometrial biopsy result at baseline
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 (NDA 11-938/S-068, volume 70.1, page 123-4)

had breast or endometrial cancer
had any other cancer except nonmelanomatous skin cancer diagnoses < 5 years before baseline
any serious medical illness
severe menopausal symptoms

4.5 Screening period

An informed consent for the study was obtained from each participant prior to the start of screening. The participants underwent pelvic examination, Papanicolaou smear, and endometrial biopsy during prestudy evaluation. Women were eligible for randomization if the results of the above studies were normal.

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 (see Table 2. 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 3 month, 6 month and 12 month examinations during the first year post-randomization and at 6 month intervals thereafter for the remainder of the 3-year study.

Table 2. Number of Women with a Uterus Assigned to Treatment Group

Treatment Groups	Number of Women
Placebo	119
0.625 mg/d CEE-Only	119
0.625 mg/d CEE + 10 mg/d Provera (for the first 12 days of each cycle)	118
0.625 mg/d CEE + 2.5 mg/d of Provera (continuous)	120
0.625 mg/d CEE + 200 mg/d of MP (for the first 12 days of each cycle)	120

CEE = conjugated equine estrogens
Provera = medroxyprogesterone acetate
MP = micronized progesterone
Source: NDA 11-839/S-068, Volume 70.1, page 23

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. Biopsy slides were reviewed by a local pathologist and followed up by an independent central reader. A third pathologist reviewed slides with a discrepancy between the local and the central reader. In most cases, the final diagnosis was based on agreement between two of the three pathologists. When there was disagreement among the three pathologists, 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.[6] 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 period

The efficacy analyses of endometrial biopsy data in the PEPI study are based on the efficacy evaluable population that 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 of all adverse events 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.

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

[6] Hendrickson M, Kempson R. Endometrial hyperplasia. Major problems in pathology. Philadelphia PA: WB Saunders; 1980;12:285-318.

year treatment period represent the worst biopsy result obtained during the 3 year study period (primary efficacy endpoint).

4.8 Withdrawals and compliance

596 women with an intact uterus were randomly assigned to one of five treatment regimens. Participants who stopped taking their medications for more than one week were recorded as interruptions in administration of study medications. Overall, a total of 444 women (74.5% of the Intent-to-Treat population) continued to take their study medications for at least 80% of the follow-up period. However, only 43.7% (n = 52) of the women assigned to the CEE-only group continued to take the study drug for at least 80% of the follow-up period compared with 80% to 85% (96 to 102 women) in the other four groups (p<001) (NDA 11-839/S-068, volume 70.1, page 25).

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.

In the PEPI study it was possible for subjects to temporarily drop from the study medication or miss a scheduled visit and continue participation in the study. Subject participation in yearly study visits was similar in the two MPA arms of the PEPI study (continuous 2.5 mg and cyclic 10 mg MPA) and the CEE alone arm for 12, 24 and 36 months. At 12 months 96.7% of the CEE + MPA 2.5 mg continuous group, 100% of the CEE + MPA 10 mg cyclic group, and 96.6% of the CEE-only group completed scheduled study visits. At 24 months 96.7%, 98.3%, and 95.8% respectively, completed visits and at 36 months 97.5% of the CEE + MPA 2.5mg continuous group, 98.3% of the CEE + MPA 10 mg cyclic group, and 96.6% of the CEE-only group completed scheduled study visits.

Endometrial biopsies declined more over time for the CEE-only treatment group than for the CEE + MPA treatment groups; only 82% (n = 98 of 119) of the CEE-only compared to 91% (n = 109 of 120) and 92% (n = 108 of 118) for 2.5 continuous MPA and 10 mg cyclic MPA respectively, had endometrial biopsies at the 36 months visit. See Table 3 prepared by the Statistical Reviewer from the PEPI data set.

Table 3: Disposition of subjects at scheduled biopsy visits (PEPI Study)

	CEE+MPA 2.5 mg continuous		CEE+MPA 10 mg cyclic		CEE only	
	n	% of rand.	N	% of rand.	n	% of rand.
Initial Biopsy (Randomized)	120	100%	118	100%	119	100%
12 Month Visit:						
Discontinued from biopsy portion before 12-month visit; no further biopsies	4	3%	2	2%	6	5%
Missing 12 month biopsy	1	1%	0	0%	3	3%
Biopsy at 12 month visit	115	96%	116	98%	110	92%
24 Month Visit:						
Discontinued from biopsy portion before 24-month visit; no further biopsies	1	1%	3	3%	6	5%
Missing 24 month biopsy	4	3%	0	0%	3	3%
Biopsy at 24 month visit	111	93%	113	96%	104	87%
36 Month Visit:						
Discontinued from biopsy portion before 36-month visit; no further biopsies	6	5%	5	4%	9	8%
Biopsy at 36 month visit	109	91%	108	92%	98	82%

Source: PEPI data set

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. Reductions 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 CEE-alone had at least one unscheduled biopsy (NDA 11-839/S-068, volume 70.1, page 26). These 79 women had 66.1% (115/174) of all unscheduled biopsies. Sixteen (13.6%/118) women taking cyclic MPA and nine (7.5%/120) taking continuous MPA had unscheduled biopsies, rates that were similar to those women receiving placebo.[1]

A total of 506 women (84.9%) had normal results for all follow-up biopsies (36 months). Endometrial hyperplasia or endometrial adenocarcinoma was reported for 90 women (15.1%). 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.[1] 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. Among the women receiving continuous CEE plus 2.5 mg MPA, one case of simple hyperplasia (1%) occurred. For women receiving continuous CEE plus cyclic 10 mg MPA for 12 days, 4 cases of simple hyperplasia (3%) and 2 cases of complex hyperplasia (2%) occurred.

Table 4 categorizes the endometrial histology results during follow-up for each participant. The proportion of patients with no hyperplasia or hyperplasia was generally similar among the estrogen-progestin combination and placebo groups. None of the women receiving the estrogen-progestin combination developed cancer of the endometrium.

Table 4. Summary of Endometrial Biopsy Changes since Normal Baseline to Most Extreme Results by Treatment Regimen during the Three-Year Treatment Period*

Endometrial Diagnosis	Number (%) of Patients					
	Placebo N=119	CEE (0.625 mg) N=119	MPA (10 mg) + CEE (Cyclic) n=118	MPA (2.5 mg) + CEE (Continuous) n=120	MP (200 mg) + CEE N=120	Total
NO HYPERPLASIA†	116 (97)	45 (38)	112 (95)	119 (99)	114 (95)	506 (84.9)
HYPERPLASIA	3 (3)	74 (62)	6 (5)	1 (1)	6 (5)	90 (15.1)
Simple (cystic)‡	1 (1)	33 (28)	4 (3)	1(1)	5 (4)	44 (7.4)
Complex (adenomatous)‡	1 (1)	27 (23)	2 (2)	0	0	30 (5.0)
Atypia‡	0	14 (12)	0	0	1 (1)	15 (2.5)
Adenocarcinoma	1 (1)	0	0	0	0	1 (0.2)

CEE = conjugated equine estrogens (administered at a dose of 0.625 mg/day); MPA = medroxyprogesterone acetate tablets (administered either for a cyclic period or continuously: cyclic = 10 mg/d X 12D; continuous = 2.5 mg/d QD); MP = micronized progesterone (administered at a dose of 200 mg/d X 12D).

* Includes 30 cases in which the diagnosis was assigned by the local gynecologist because the local, central, and arbiter pathologists gave different opinions.

† p = .16 (normal vs. abnormal) for placebo compared with CEE + PROVERA (cyclic), CEE + PROVERA (continuous), and CEE + MP.

‡ p<.001 for placebo compared with CEE-only.

Source: Adapted from NDA 11-839/S-068, Volume 70.1, page 27

4.10 Safety analysis

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.[1] The majority of women with a diagnosis of simple hyperplasia (a total of 38 [86%] of 44 women) reverted to normal with or without intervention; 5 (11%) women persisted with this diagnosis at subsequent biopsies and 1 (2%) had incomplete follow-up data.

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.

Of the 45 women with complex (adenomatous) or atypical hyperplasia, study medications were discontinued in all, and the biopsy results of 34 (94%) of 36 women with hyperplasia reverted to normal with progestin therapy. The remainder had dilatation and curettage (n=2) or hysterectomy with (n=2) or without (n=6) prior medical therapy, or refused further biopsies (n=1). One woman developed adenocarcinoma of the endometrium while receiving placebo.[1]

The PEPI study data show a significant difference ($p<.001$) in the hyperplasia-free intervals among the regimens. Women in the placebo and combined CEE plus progestin groups had longer intervals free of all three types of hyperplasia (simple, complex, or atypia) than women in the CEE-only group. At 36 months, 62.2% (n=74 of 119) of women in the CEE-only group developed some type of hyperplasia, 34.5% (n=41 of 119) had the more concerning diagnosis of complex (adenomatous) or atypical hyperplasia (see Table 7 in the Statistical Review and Evaluation report). The majority of women with a diagnosis of simple hyperplasia (a total of 38 [86%] of 44 women) reverted to normal with or without intervention; 5 (11%) women persisted with this diagnosis at subsequent biopsies and 1 (2%) had incomplete follow-up data. The one women with a diagnosis of adenocarcinoma had a hysterectomy and bilateral salpingo-oophorectomy and has remained free of the disease since surgery per the authors.[1]

The development of all three types of hyperplasia remained relatively constant over the three years of treatment in the PEPI study. The Writing Group for PEPI anticipates that a majority of women taking CEE alone would have the more serious type of complex or atypical hyperplasia after about five years of therapy.

4.11 Summary of DSI audit

No clinical inspections are required.

5. The Menopause Study Group

5.1 Objectives/rationale

Although progestins are frequently prescribed as part of hormone replacement therapy, there are few large randomized controlled trials on which to base the selection of the appropriate dosages.[7] The purpose of this one year study in healthy postmenopausal women was to "evaluate four oral combinations of conjugated estrogens (Premarin®) and medroxyprogesterone acetate (MPA) in comparison with conjugated estrogens alone with a sufficiently large population to establish statistically significant differences in the incidence of endometrial hyperplasia."[2] Other parameters evaluated in this study included bleeding profiles and metabolic safety.

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[7] Harlap S. The benefits and risks of hormone replacement therapy: an epidemiologic overview. Am J Obstet Gynecol 1992;166:1986-92.

5.2 Design

The Menopause Study Group was a prospective, double-blind, parallel, controlled, multicenter study conducted with 1724 postmenopausal women at 99 sites in the United States and Europe over a one year period. Generally healthy women who were 45 to 65 years old with an intact uterus were eligible for the study. All subjects had at least 12 months of spontaneous amenorrhea and a serum follicle-stimulating hormone (FSH) concentration higher than the lower limit for postmenopausal women for the given laboratory (usually between 25 and 35 mIU/ml). A two-week wash out period was required for prior estrogen or progestin use. Patients were randomly assigned to one of five treatment groups for 13 cycles. There was no placebo group.

The dosage regimens and the number of women assigned to each regimen are shown in Table 5.

Table 5. Dosage Regimens and Number of Women Assigned to Treatment Group

Regimen	Cycle days	CEE (mg)	MPA (mg)	Number of women Randomized
A	1-28	0.625	2.5	345
B	1-28	0.625	5.0	345
C	1-14	0.625	Placebo	
	15-28	0.625	5.0	345
D	1-14	0.625	Placebo	
	15-28	0.625	10.0	345
E	1-28	0.625	Placebo	345

CEE = conjugated estrogen; MPA = medroxyprogesterone acetate
Source: NDA 11830/S-068, Volume 70.1, page 30

Premarin® 0.625 mg taken daily was selected as the minimum effective dosage of estrogen to prevent bone loss.[8] Medroxyprogesterone acetate or a matching MPA placebo was taken orally at the same time each day. Regimens A and B were continuous combined regimens given each day of a 28 day cycle (Regimen A = 0.625 mg CEE and 2.5 mg MPA; Regimen B = 0.625 mg CEE and 5 mg MPA). Regimens C and D were sequential regimens (Regimen C = 0.625 mg CEE days 1-28, placebo days 1-14 and 5 mg MPA days 15-28; Regimen D = 0.625 mg CEE days 1-28, placebo days 1-14 and 5 mg MPA days 15-28). Regimen E was conjugated estrogen and placebo days 1-28. provided all study medication. Each patient was given diary cards for daily recording of tablets taken or omitted.

Scheduled endometrial biopsies were performed before treatment at baseline, during days 22 to 28 of cycles 6 and 13, or anytime if medically indicated. Endometrial tissue was obtained with a Pipelle cannula, the Novak curette, or the Vabra aspirator in approximately 75% of the biopsies performed. The other 25% were obtained with 14 other uterine endocervical curettes.

One pathologist reviewed all biopsy slides. Biopsy results were classified as follows: cystic or adenomatous hyperplasia without atypia; or cystic or adenomatous hyperplasia with atypia. Woodruff and Pickar indicate that this classification corresponds to the alternative classification of simple hyperplasia, complex hyperplasia; simple atypical or complex atypical hyperplasia, respectively.[2]

Reviewer's Comment

The Menopause Study Group study design fails to meet the 1995 Guidance for Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products used for Hormone Replacement Therapy for Postmenopausal Women in three areas. First, the guidance stipulates, for endometrial protection studies, a washout period before baseline assessment of at least 8 weeks for prior oral estrogen and/or progestin therapy, and at least 4 weeks for prior transdermal therapy. The short,

[8] Lindsay R, Hart DM, Clark DM. The minimum effective dose of estrogen for prevention of postmenopausal bone loss. Obstet Gynecol 1984;63:759-63.

"at least two weeks", washout period observed before the prestudy screening may have resulted in exogenous hormone being present from the previous therapy. Although not ideal, it is unlikely that this short washout period influenced results.

Second, twenty-five percent of all endometrial biopsies were obtained with one of fourteen different curettes. However, 75% of biopsy specimens were obtained with the Pipelle cannula, Novak curette or the Vabra aspirator, which is consistent with the PEPI Study. When no tissue or no endometrial tissue was obtained at biopsy in The Menopause Study Group study these women were classified as normal due to presumed atrophy. The article does indicate that approximately 20% of the biopsy specimens obtained from women taking the continuous combined regimens (groups A & B in Table 4); 10% of biopsy specimens for groups C & D; and 15% of biopsy specimens in group E, had no tissue or no endometrial tissue identified. No information provided explains whether these findings were possibly due to suboptimal instruments and/or inexperienced operators. Nonetheless, the percent of biopsy specimens with no tissue or no endometrial tissue were relatively balanced between study arms.

Thirdly, only one pathologist read the endometrial biopsy slides. Per the guidance, two independent pathologists blinded to treatment group assignments and a third independent pathologist to adjudicate their diagnostic differences are requirements for an endometrial protection indication. In this case, Dr. Woodruff, a highly regarded, published (author of journal articles and textbook chapters on gynecologic histology) pathologist solely read each biopsy slide using histology criteria and terminology reported in Blaustein's Pathology of the Female Genital Tract and in Novak's Gynecologic and Obstetric Pathology. This reviewer credits Dr. Woodruff's extensive experience and expertise as the single pathologist in The Menopause Study Group study.

The aforementioned three issues, while not major concerns, do make The Menopause Study Group study somewhat less ideal than the PEPI study as a supportive trial for this indication.

5.3 Study population

A total of 1724 postmenopausal women were randomly assigned to the five treatment regimens. Ninety six to ninety eight percent of the patients in each treatment group were White; two to five percent were black. The average patient age was 54 years with 5.3 years duration of menopause. Their mean weight was 64kg. Demographic characteristics for the study population were almost identical ($p<0.05$) for each of the treatment groups.

5.4 Inclusion and exclusion criteria

Woodruff and Pickar list no specific inclusion and exclusion criteria in the published article with the exception of the following limited inclusion information:

- Age between 45 to 65 years
- Intact uterus
- Last natural menstrual cycle at least 12 months before baseline screening
- Serum follicle stimulating hormone concentration higher than the lower limit for postmenopausal women for the given laboratory
- No use of any estrogen- or progestin-containing medication for at least two weeks prior to screening

5.5 Screening period

An informed consent for the study was obtained from each participant prior to enrollment in the study. No additional information regarding parameters of the screening period is available.

5.6 Treatment period

Eligible subjects were randomized in a double-blinded fashion to the 5 arms of the study. See Table 4 on page 11 of this review. Patients were given diary cards for the daily recording of tablets taken or omitted. Investigator permission was required for use of any concomitant medication other than oral calcium.

Patients were prohibited from taking any estrogen or progestin other than the trial medication during the study. Other steroids were restricted to no more than 10 total days of use during the 12-month study.

Scheduled endometrial biopsies were performed at baseline and during Days 22 to 28 of cycles 6 and 13. Approximately 75% of biopsies were performed using a Pipelle, Novak, or Vabra curette. The remaining 25% were obtained with one of fourteen other curettes.

. If an endometrial biopsy indicated endometrial hyperplasia the patient was withdrawn from the study and given appropriate therapy (NDA 11-839/S-068, Volume 70.1, page 30).

5.7 Evaluation period

The efficacy analyses of endometrial biopsy data in the Menopause Study Group are based on the efficacy evaluable population which includes all randomized patients who had a pretreatment endometrial biopsy, had taken at least one dose of study medication, and either underwent an endometrial biopsy during cycles 12 to 14 or had endometrial hyperplasia in an earlier cycle.[2] Data for these patients were included in the 12-month analysis. Of the 1724 women who enrolled in the study, 1385 patients completed the study with endometrial biopsy data valid for analysis at 12 months.

The Fisher's exact test was used to compare the incidence of endometrial hyperplasia between the CEE alone group and each CEE/MPA group. Six and 12 months comparisons were completed. All pairwise comparisons were made by use of two-sided tests. A Bonferroni adjustment for the four multiple comparisons was made in the significance levels.

5.8 Withdrawals and compliance

Per the sponsor and the published article, when an endometrial biopsy performed during the study indicated endometrial hyperplasia, the patient was withdrawn from the study. Sixty-two women developed endometrial hyperplasia during the study. All of these women stopped taking the trial medication and were withdrawn from the study. Fifty-five of these women were treated hormonally (treatment not specified); seven women were not treated hormonally. One patient was lost to follow up. No additional information on patient withdrawal or compliance is available.

5.9 Efficacy analysis

A total of 1323 women (96%) of the 1385 patients randomized for all treatment groups had normal results for follow-up biopsies at 12 months. Endometrial hyperplasia was reported for 62 women (4%) in the evaluation of the 12-month data (which included the 6-month data). The incidence of hyperplasia and the results of the statistical comparison by treatment group or the 12-month data are presented in Table 6 below.

Table 6. Incidence of endometrial hyperplasia at 12 months (6 and 12 months evaluations combined)

0.625 mg CEE* + MPA as Indicated:	No. of Patients	Patients with Positive Specimens for Hyperplasia No. (%)	Comparison with Conjugated Estrogens Alone† p-value
Regimens			
A 2.5 mg (days1-28)	279	2 (<1)	p<.001
B 5 mg (days 1-28)	274	0 (0)	p<.001
C 5 mg (days 15-28)	277	3 (1)	p<.001
D 10 mg (days 15-28)	272	0 (0)	p<.001
E No MPA	283	57 (20)	--
Total	1,385	62	--

* All groups received conjugated estrogen 0.625 mg every day of a 28-day cycle

† Based on Fisher's exact test

Source: NDA 11-938/S-068, Volume 70.1, page 31

The incidence of endometrial hyperplasia was significantly lower with each of the conjugated estrogen/medroxyprogesterone acetate treatment groups than with conjugated estrogen alone. The estrogen-alone treatment group had an incidence of endometrial hyperplasia of 7% at 6 months and 20% at 12 months. In comparison, only 1% or fewer patients in the estrogen plus MPA treatment groups developed endometrial hyperplasia during the entire 12 month study.

There were a total of five cases of endometrial hyperplasia in the two lower-dose MPA treatment groups (Regimen A = 0.625 mg CEE plus 2.5 mg MPA continuously and Regimen C = 0.626 mg CEE days 1-28 plus 5 mg MPA days 15 –28). At six months, Regimens A and C each showed one case of hyperplasia. At the end of the 12-month study, one additional case of endometrial hyperplasia was documented in Regimen A and two additional cases in Regimen C. No hyperplasia was reported in the two higher-dose treatment groups (Regimen B = 0.625 mg CEE plus 5 mg MPA continuously and Regimen D = 0.625 mg CEE days 1-28 plus 10 mg MPA days 15-28) at either the 6 month or the 12 month evaluations. Fifty-seven cases of endometrial hyperplasia were diagnosed by 12 months in the estrogen alone regimen, Regimen E, which included 0.625 mg conjugated estrogens continuously (21 cases at 6 months and an additional 36 cases by 12 months for a total of 57 cases). Woodruff and Pickar suggest that the lower dosages of MPA (2.5 mg continuously or 5 mg given for 14 days per cycle) utilized in the Menopause Study Group study are the minimum required to counteract the endometrial effects of continuous therapy with 0.625 mg of conjugated estrogens.[2]

Fifty-five of the 62 women who developed endometrial hyperplasia during the study were treated hormonally (treatment not specified) and had negative follow-up biopsy specimens. Seven women who were diagnosed with endometrial hyperplasia were not treated hormonally. However, six of these seven women had follow-up biopsies that were negative for endometrial hyperplasia. Cervical stenosis prevented a successful biopsy attempt in the seventh patient.

Additionally, two women developed endometrial cancer diagnosed at their one-year follow-up biopsy. One patient in treatment Regimen D (0.625 mg CEE days 1-28 plus 10 mg MPA days 15-28) was diagnosed with adenocarcinoma, endometrioid type, grade 2. The other patient had taken Regimen E (continuous estrogen alone) and was diagnosed with adenocarcinoma of the endometrium, grade 1. Both patients underwent hysterectomy.

5.10 Safety Analysis

Per Woodruff and Pickar, if an endometrial biopsy performed during the study indicated hyperplasia, the patient was withdrawn from the study and given appropriate therapy. Most of the 62 women in whom endometrial hyperplasia developed during the study were treated "hormonally" (no specific information is provided in the published literature submitted). There were no reported cases of endometrial cancer in follow-up biopsies of the women who had endometrial hyperplasia.[1]

Other parameters evaluated in the study included bleeding profiles and metabolic safety. An article regarding bleeding profile data is in press. Metabolic safety data in "on file" per Woodruff and Pickar. No other adverse event information is found in the published article submitted with the application.

5.11 Summary of DSI Audit

No clinical inspections are required.

6. Labeling review

A labeling meeting was held on July 31, 1998 to review the proposed labeling for Provera®. Please see Attachment 2 for the meeting minutes and the required labeling changes.

Reviewer's comment

In January 1998, the sponsor submitted Amendment 001 to the efficacy supplement to NDA 11-839/S-068 in response to the Division concern that the data would only support the sequential use of

Provera® to suppress endometrial hyperplasia and carcinoma induced by Premarin® and not by all estrogens as a class. Their "argument" centered on the general ability of all estrogen substances to induce endometrial hyperplasia and carcinoma and that progestins as a class, to which Provera® belongs, have the ability to suppress the hyperplasia.

The two studies in this submission utilized MPA (sequential or continuous combined regimens) with conjugated estrogens which is a mixture of numerous estrogenic compounds. Amendment 001 provides additional literature supporting the sequential use of MPA with transdermal estradiol (E2). Only one case of hyperplasia (in 190 evaluable women) was found in four studies of patients on transdermal E2 plus Provera® over a two year period (NDA 11-839/S-068, Amendment 001, pages 1-3). One two-year study comparing continuous transdermal E2 (0.1 mg) given alone with continuous E2 plus 10 mg MPA for 12 days, found endometrial hyperplasia in 11 of 22 evaluable patients in the E2 alone group and one case of hyperplasia (1/26) in the E2 plus MPA group. Another study comparing 0.05 mg E2 daily plus 10 mg MPA/day for 10 days with 0.05 mg E2 daily plus 0.25 mg norethindrone acetate/day for 14 days for 13 cycles found one case of hyperplasia with E2 plus norethindrone acetate and no cases of hyperplasia with E2 plus MPA. At the end of two studies there was no evidence of hyperplasia in any patient.

Based on this information, the sponsor feels that "Provera® is safe and effective in suppressing endometrial hyperplasia for estrogens as a class when appropriate doses are used." However, no specific data has been presented for Provera® use with estrogens such as ethinyl estradiol and esterified estrogens and the large pivotal Phase 3 trial submitted for this indication only included conjugated estrogens (Premarin®).

7. Reviewer's assessment of safety and efficacy

This NDA 11-839/S-068 presents published literature information in support of the safety and efficacy of medroxyprogesterone acetate (MPA) in combination with conjugated equine estrogen (CEE) for the prevention of endometrial hyperplasia in women with a uterus. Data from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial and The Menopause Study Group study was commented upon by the sponsor, Pharmacia and Upjohn. In the PEPI study (a large, prospective, randomized, double-blind, placebo-controlled, multicenter study of 875 postmenopausal women, 596 with a uterus), the primary efficacy endpoint was the worst endometrial histology assessment based on the endometrial biopsies in women with a uterus over the three year treatment period. In The Menopause Study Group study (a large, prospective, randomized, double-blind, multicenter study of 1724 postmenopausal women with a uterus), the primary efficacy endpoint was the worst endometrial histology based on the endometrial biopsies in women with an intact uterus over a one year treatment period. The comparison of MPA + CEE versus CEE alone was identified as the primary efficacy comparison for both studies. The Menopause Study Group study did not contain a pure placebo arm.

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 a uterus increases the risk of endometrial hyperplasia, a possible precursor of endometrial adenocarcinoma. The addition of a progestin to estrogen therapy for at least 10 days per cycle effectively reduces the risk of endometrial hyperplasia and subsequently of endometrial cancer.[9]

MPA was effective in the prevention of endometrial hyperplasia in women with a uterus who took CEE. In the PEPI study, the number of women being treated with 0.625 mg CEE (days 1-28) plus 10 mg MPA (days 1-12) who developed endometrial hyperplasia by the 36 month time point was statistically lower in this CEE + MPA group compared to the CEE alone group, 5% compared to 62 %, based on the final 36

[9] Lobo RA. The role of progestins in hormone replacement therapy. Am J Obstet Gynecol 1992;166:1997-2004.

months analysis. In The Menopause Study Group study, the number of women being treated with 0.625 mg CEE (days 1-28) plus 5 mg MPA (days 15 –28) who developed endometrial hyperplasia by the 12 month time point was statistically lower in this CEE + MPA group compared to the CEE alone group, 1% compared to 20% based on the final 12 months analysis (see Statistical Review and Evaluation). For the treatment group receiving 0.625 mg CEE (days 1-28) and 10 mg MPA (days 15-28), no women (0%) developed endometrial hyperplasia by the 12 month time point compared to 20% for the CEE alone group.

The key studies and supportive literature submitted with this application support the conclusion that medroxyprogesterone acetate (MPA) provides protection from endometrial hyperplasia in women with an intact uterus who are receiving estrogen replacement therapy.

Reviewer's comment

The two published studies submitted with this application both contain a continuous 0.625 mg CEE + 2.5 mg MPA (days 1-28) treatment arm for which approval was not requested. The Menopause Study Group study also included a continuous 0.625 mg CEE + 5 mg MPA treatment arm for which approval was not requested. It is interesting to note that in the PEPI study, the percent of study participants assigned to the continuous 0.625 mg CEE + 2.5 mg MPA regimen that developed endometrial hyperplasia was lower compared to the cyclic CEE + 10 mg MPA arm at 36 months, (1% compared to 5%). In The Menopause Study Group study, the percent of study participants assigned to the continuous 0.625 mg CEE + 2.5 mg MPA treatment arm that developed endometrial hyperplasia at the 12 month time point was slightly lower compared to cyclic 5 mg MPA (<1% compared to 1%) but was higher when compared to the cyclic 10 mg MPA arm (<1% compared to 0%). In the continuous 0.625 mg CEE + 5 mg MPA treatment arm the women that developed endometrial hyperplasia at the 12 month time point was lower compared to the cyclic 5 mg MPA arm (0% compared to 1%) and equal to the cyclic 10 mg MPA arm (no hyperplasia developed in either arm). The sponsor has offered no explanation regarding why they have not requested approval for the continuous 2.5 or 5 mg MPA dose.

The duration of progestin use each month needed to protect the endometrium from the proliferative effects of estrogen is an important variable in estrogen/progestin combination therapy in non-hysterectomized postmenopausal women. The PEPI Trial results support a 10 mg/day dose of MPA for 12 days (and a 2.5 mg /day dose of Provera throughout the cycle) as adequate to protect the endometrium in women with uteri receiving estrogen replacement therapy. Doses of 5 mg/day and 10 mg/day of MPA for 14 days of a 28-day cycle (and 2.5 mg and 5 mg MPA continuously for days 1-28) were shown to be protective in The Menopause Study Group study. The sponsor believes this data support the following dose recommendations for Provera®:

- **10 mg given for 12 to 14 consecutive days/cycle, or**
- **5 mg given for 14 consecutive days/cycle (NDA 11-839/S-068, Volume 70.1, page 40).**

In addition, The Committee on Gynecological Practice of the American College of Obstetricians and Gynecologist concluded "that when medroxyprogesterone is used for hormone replacement therapy, 5.0 mg should be the standard dose for the cyclic regimen (except for women with persistent heavy withdrawal menses) and 2.5 mg for the continuous combined regimen."[10]

[10] Andrews WC. Progestin dosage in hormone replacement therapy. ACOG Clinical Review 1996;1:1,14.

7. Recommended regulatory action

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

/S/

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

I concur /S/

Attachments: Attachment 1: Regulatory History, NDA 11-839
Attachment 2: Labeling Meeting Minutes and Required Labeling Changes

CC: NDA 11-839 Division File
HFD-580/JMarkow/MMann/TvanderVlugt

Attachment 1. Regulatory History, NDA 11-839

Status Date: July 20, 1998

NDA 11-839

Drug: PROVERA® (medroxyprogesterone acetate)
Sponsor: Pharmacia & Upjohn
Indication: Secondary amenorrhea; abnormal uterine bleeding due to hormone imbalance in the absence of organic pathology, such as fibroids or uterine cancer.

Regulatory History

April 8, 1983 Submission from sponsor requesting approval to add following adverse reactions to label: anaphylactoid reaction and anaphylaxis, pyrexia, insomnia, nausea, and somnolence.

May 31, 1983 Letter to Upjohn Company from DMEDP Director; supplemental new drug application submitted on 2/28/83 requesting revision of the adverse reaction section of the labeling: change proposed is permitted but formal action will be deferred pending review of previous supplemental application.

July 19, 1983 Letter to sponsor from DMEDP Director; request information on the bases on which decisions were made to include each of the following reactions in the labeling: anaphylactoid reaction and anaphylaxis, pyrexia, insomnia, nausea, and somnolence.

Oct. 6, 1983 Medical Officer's review of final labeling; approval of the final printed labeling is recommended.

Nov 22, 1983 Sponsor submits final printed package insert that adds above adverse reactions.

April 25, 1984 Medical Officer's review of final printed package insert; approval of the labeling is recommended.

July 31, 1984 Memo of meeting with sponsor to discuss deficiencies in the supplemental NDA for Provera 50 mg tablets for treating recurrent breast cancer: two well-controlled studies are required to approve a drug; study designed to determine regression of disease is not of sufficient duration; total number of evaluable patients at 400 mg and 800 mg may be too small; study should include a common regimen of chemotherapy for treatment failures.

Feb. 12, 1985 S-046 from sponsor provides for deleting

Sept. 26, 1985 Memo of meeting with sponsor to discuss the requirements for submission of NDA for a combined estrogen and Provera Tablet for abnormal uterine bleeding indication; the Agency has not yet made a decision as to whether the combination therapy to prevent hyperplasia should be included in the labeling for these drugs; if decision made to do so then the proposed combination package for Provera and an estrogen could be approved on the basis of the more global indication.

Nov 1, 1985 Letter to sponsor; S-046 is approved.

July 18, 1986 Memo of meeting with sponsor to discuss their protocol for comparing sequential estrogen and progestin with continuous administration; there is a need for planned

statistical analysis; recommended that lipids be evaluated at 3 and 9 months and repeat biopsies before 1 year; addition of an estrogen only group would make a stronger study.

Aug. 19, 1986 Submission containing description of how sample size was determined for Protocol M54100089.

Feb. 6, 1997 Letter to sponsor regarding 8/19/96 submission; sample sizes should be calculated based on 2-sided test; number of patients actually required at the beginning of randomization should be specified.

Sept. 8, 1987 Sponsor submits S-050, Special Supplement Changes Being Effected.

Oct. 26, 1987 Letter to sponsor from DMEDP Director regarding S-050; we have completed our review of the submitted final labeling and it is acceptable; the INDICATIONS section should be changed to INDICATIONS and USAGE.

Dec. 21, 1986 Medical Officer's review of submission dated 5/29/97; approval of the supplement for treatment of endometriosis is not recommended.

Feb. 15, 1988 S-052 form sponsor provides for alternate packaging location.

June 3, 1988 Letter to sponsor from Director regarding S-052; supplement is approved.

Jan. 13, 1989 Medical epidemiologist increased frequency report: number of thromboembolic phenomena for 5/31/86-5/30/87 = 8 (comparative period 1985-1986 = 3; "don't believe this represents a true instance of increased frequency; no further action is planned.

May 26, 1989 Statistical review and evaluation of Protocol M54100159: this study can achieve only limited objective = the effect of Provera on the lipid profiles of postmenopausal, hysterectomized women.

June 20, 1989 Letter to sponsor from DMEDP Director which conveys Biometrics review.

Aug. 11, 1989 Division letter to sponsor: supplemental application is withdrawn.

Oct. 6, 1989 Division letter to sponsor: S-053 is approved providing for an alternate manufacturing site in Puerto Rico.

Oct. 30, 1990 Letter from Division Director to Upjohn: "Your promotional material concerning this

sponsor offered opportunity to voluntary this approved supplement.

Oct. 31, 1990 Letter to sponsor from the Division of Drug Advertising and Labeling:

Nov. 19, 1991 Division letter regarding supplement providing changes in the carton labeling of the complimentary physician packages: final printed label is approved.

Dec. 18, 1991 Division letter regarding S-058 and the subsection under PRECAUTIONS regarding carcinogenesis, mutagenesis, and impairment of fertility: approved.

March 15, 1993 Chemist's Review of S-062 providing for a change in packaging of the 2.5 mg and 5 mg tablets from bottles to blister packs: supplement is recommended as approvable.

April 30, 1993 Division letter to sponsor: S-062 is approved.

June 2, 1993 Chemist's Review of DMF (bulk drug): the DMF files are satisfactory to support the listed supplements in the review.

June 3, 1993 Chemist's Review of S-061 submitted 8/24/92 regarding replacement of supplement is approvable.

June 3, 1993 Chemist's Review of S-063 submitted 9/1/92 regarding a change in packaging from glass bottles with tin-plate caps to HDPE bottles with polypropylene caps: supplement is approvable.

June 23, 1993 Division letter to sponsor approving S-061 and S-063.

Dec. 16, 1993 Division letter regarding review of package insert sent May 12, 1993; recommend changes: incorporate a subsection on Nursing mothers under the PRECAUTIONS section.

July 25, 1995	Memo to the file: labeling for NDA 11-839 could remain as it presently is with a class labeling statement in the WARNINGS section; a separate statement regarding nursing mothers did not have to be added to the PRECAUTIONS section.
Nov. 22, 1995	Chemist's Review of SCS-066 providing for a change in the analytical method of assay, method which is similar to the current USP method: CMC are adequate; approved.
Nov. 28, 1995	Division letter to sponsor: S-066 is approved.
March 11, 1996	Division letter to sponsor: S-062 (final printed labeling) is acceptable.
Sept. 24, 1996	SLR-067 from sponsor: change in sponsorship name from The Upjohn Company to Pharmacia and Upjohn.
Jan. 7, 1997	Clinical Pharmacology and Biopharmaceutisc Review of NDA 11-839/SN 001 submitted May 1, 1996 regarding alternative proposal for bioequivalence including two studies in support of the development of the direct compression formulation; recommendation: the proposed approach for assessing bioequivalence is not acceptable; recommend the sponsor use the Agency's "Individual Bioequivalence" approach using a four-period crossover study design.
March 28, 1997	Division letter to sponsor regarding section of progestin drug labeling that refer to concomitant use of progestins in estrogen replacement therapy; recommend under PRECAUTIONS section: delete item 10 and propose a statement to address the effects of MPA on lipid and carbohydrate metabolism (glucose tolerance).
April 29, 1997	Division acknowledges change in sponsorship name.
July 31, 1997	Sponsor submits NDA 11-839/S-068; proposed indication: reduce the incidence of endometrial hyperplasia and endometrial carcinoma in nonhysterectomized postmenopausal women.
Sept. 16, 1997	Minutes of teleconference with sponsor; decisions reached: sponsor will provide feedback to the Agency on the labeling issue (use of "estrogen replacement therapy" instead of Premarin®); and sponsor verified that the wet-granulation will be used and that they have no immediate plans to change the process.
Jan. 8, 1998	Sponsor submits Amendment 001 to NDA 11-839/S-068 providing arguments in support of the use of Provera® with estrogens in the labeling.
July 7, 1998	Statistical Review and Evaluation; Conclusion: the results of the PEPI and Woodruff studies "support the conclusion that MPA provides protection from endometrial hyperplasia in women with an intact uterus who are receiving CEE hormone replacement therapy."

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 11839/S68

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUN 24 1998

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA 11-839

SUBMISSION DATES: July 3, 1997
July 31, 1997

Provera® Tablets
(Medroxyprogesterone Acetate)
Pharmacia & Upjohn
Kalamazoo, MI

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: NDA- Clinical Supplements No. 068

BACKGROUND:

The original NDA 11-839 for Provera® Tablets was approved by the Agency on June 18, 1959 for the treatment of secondary amenorrhea and for abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer. Provera® Tablets contain medroxyprogesterone acetate (MPA), which is a derivative of progesterone. Each Provera Tablet for oral administration contains 2.5 mg, 5 mg, or 10 mg of MPA.

SUBMISSIONS:

On July 31, 1997 the sponsor submitted supplement No. 068 to NDA 11-839 which includes published clinical information to support an additional labeling indication: "use of cyclic Provera, to reduce the incidence of endometrial hyperplasia and endometrial carcinoma in nonhysteroctomized postmenopausal women receiving estrogen replacement therapy".

Supplement No. 068 provides:

- Published efficacy results from two trials (PEPI and Postmenopausal Study Group) using 12-14 days each month of MPA in combination with continuous estrogen replacement therapy.
- Published safety references on the prevention of estrogen induced endometrial hypertrophy and carcinoma by progestins, effect of combined estrogen and progestin therapy on cardiovascular risk factors, bone mineral density, and the risk of breast cancer.
- A revised version of Provera's labeling which includes clinical data for the proposed additional indication.

PEPI TRIAL SUMMARY:

Reference: Writing Group for the PEPI Trial: "Effects of hormone replacement therapy on endometrial histology in postmenopausal women". JAMA 1996a;275:370-5

The PEPI trial was a NIH-sponsored, 3-year, 7-center, randomized, placebo-controlled, parallel trial evaluating the histological findings of the endometrium of postmenopausal women who were randomized to receive placebo, estogen-only, or one of three estrogen plus progestin (E+P) regimens. A total of 596 women who were 45 to 65 years of age with an intact uterus participated in the endometrial study. The results of this study showed that 10 mg/day of Provera for 12 days per month or 2.5 mg/day of Provera throughout the cycle was adequate to protect endometrium.

POSTMENOPAUSAL GROUP TRIAL SUMMARY:

Reference: Woodruff JD., Pickarr JH: "Incidence of Endometrial Hyperplasia in Postmenopausal Women Taking Conjugated Estrogens (Premarin®) with medroxyprogesterone acetate or conjugated estrogens alone (The Postmenopausal Study Group), Am J Obstet Gynecol 1994; 170:1213-23.

This trial was a 1-year, double-blind, randomized, multicenter study in 1,724 postmenopausal women. Four combinations of conjugated estrogens (Premarin) and MPA were evaluated in preventing endometrial hyperoplasia. The study population consisted of healthy postmenopausal women who were 45 to 65 years of age and who had an intact uterus. The results showed that doses of 10 mg/day for 14 days and 5 mg/day for 14 days were appropriate to reduce the incidence of hyperplasia to <1% when combined with estrogen therapy.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed supplements 068 to NDA 11-839 submitted on July 3 and July 31, 1997, respectively, for Provera® Tablets. The Reviewer Comments for these submissions are as follows;

1. The clinical supplement No. 068 to NDA 11-839 does not include any new clinical pharmacology and biopharmaceutic information for this product. Therefore, no additional recommendations to the ones given in the previous approvals (original and others) are made at this time.

2. Supplement No. 068 does not include any drug-drug interaction information for the studied combination of Provera® and Premarin®. This lack of drug-drug information is clearly

indicated in Provera's labeling; **"No formal pharmacokinetic *drug-drug* interaction studies have been conducted with Provera".**

3. It should be noted that the Drug-Drug Interaction subsections of Prempro™ and Premphase™ labeling (conjugated estrogens/MPA tablets) include the statement **"Coadministration of conjugated estrogens with MPA does not affect the pharmacokinetic profile of MPA; similarly, MPA does not affect the pharmacokinetic profile of the conjugated or unconjugated estrogens".** Therefore, it appears to be appropriate to recommend that a similar drug-drug interaction statement be included in Provera's labeling.

4. It should be noted that the labeling provided in supplement No. 068 does not include a **"Clinical Pharmacology"** section or a **"Pharmacokinetic"** subsection. However, supplement provides a new draft labeling. The revision consists of the replacement of the **"ACTIONS"** section of the package insert with a **"CLINICAL PHARMACOLOGY"** section and a **"Pharmacokinetic"** subsection. Therefore, it is recommended that the same revision be made in the labeling proposed in supplement No. 068.

5. The following changes are recommeded for the **Pharmacokinetic** subsection of the proposed new draft labeling provided in supplement

Pharmacokinetics

TABLE 1. PHARMACOKINETIC PARAMETERS FOR MEDROXYPROGESTERONE ACETATE

REVIEWER COMMENT: SPONSOR SHOULD COMPLETE TABLE 1 and A LEGEND UNDER TABLE 1 SHOULD DEFINE THE THE PHARMACOKINETIC PARAMETERS LISTED IN THE TABLE.

Distribution: Proposed text is appropriate

Metabolism: Proposed text is appropriate

Excretion: Proposed text is appropriate

Special Populations:
Proposed text is appropriate

Drug-Drug Interactions: No formal pharmacokinetic drug-drug interaction studies have been conducted with PROVERA. However, published literature indicates that coadministration of conjugated estrogens with MPA does not affect the pharmacokinetic profile of MPA; similarly, MPA does not affect the pharmacokinetic profile of the conjugated or unconjugated estrogens. Literature data also indicate that concomitant administration with aminogluthimide would significant reduce serum concentrations of MPA, likely by increasing the clearance of the drug.

Please convey the Recommendation and Labeling Comment No. 5 as appropriate to the sponsor.

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD Initialed by John Hunt. JPH 6/24/98
FT signed by John Hunt. 6/24/98

cc: NDA 11-839, HFD-580 (van der Vlugt, Moore), HFD-870 (Chen, Dorantes), CDR (Barbara Murphy for Drug).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 11839/S68

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical Studies

Date: JUL - 7 1998

NDA #: 11-839 / SE1-068

Applicant: Pharmacia & Upjohn

Name of Drug: Provera (medroxyprogesterone acetate MPA) tablets

Indication: Prevention of endometrial hyperplasia in non-hysterectomized post-menopausal women who are receiving conjugated estrogens tablets

Documents Reviewed: Supplement Vol. 1; PEPI data set

Statistical Reviewer: Kate Meaker, M.S. (HFD-715)

Medical Input: Theresa van der Vlugt, M.D. (HFD-580)

Summary of Studies

The NDA submission includes literature reviews for 2 clinical trials. The PEPI study will be considered as the primary efficacy study for this review. The Medical Officer considers the second study (Woodruff) as supportive information only primarily due to how the endometrial biopsy data was collected.

The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial is a 3-year, prospective, placebo-controlled, double-blind, multicenter study which was sponsored by NIH. Subjects were post-menopausal women, ages 45-64, who were randomly assigned to receive one of five hormone replacement therapies (HRT) for up to 3 years of treatment. The treatment groups are listed in Table 1. The applicant for this NDA (Pharmacia & Upjohn) provided the medroxyprogesterone acetate (MPA) tablets used for two treatment groups in the PEPI trial. The data for the PEPI study was available for this review.

The second study, The Menopause Study Group (Woodruff Study), was a 1-year, double-blind, randomized, multicenter trial conducted by Woodruff (1994). The patient population was post-menopausal women, ages 45-65. Subjects were randomly assigned to receive one of five hormone replacement therapies (HRT) for up to 1 year of treatment. The treatment groups are listed in Table 1.

Table 1: Summary of Randomized, Controlled Studies

Study Number (Dates Conducted)	Number of Centers (Locations)	Total Sample Size	Type of Control	Design	Duration of Treatment
PEPI (12/89 - 2/94)	7 (all U.S)	875 total subjects 596 total for primary effic. analysis (with uterus) CEE+MPA 2.5 mg cont.=120 CEE+MPA 10 mg cyclic =118 CEE only = 119 Placebo = 119 CEE+MP=120	placebo and active-control treatment arms	randomized, double-blind, multicenter, parallel arms	3 years
Menopause Study Group (Woodruff; 1994)	99 (U.S & Europe)	1724 total subjects CEE+MPA 2.5 mg cont. =345 CEE+MPA 5.0 mg cont. =345 CEE+MPA 5.0 mg cyclic=345 CEE+MPA 10.0 mg cyclic=345 CEE only = 345	active-control	randomized, double-blind, multicenter, parallel arms	1 year

PEPI STUDY

Background

The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial is a clinical study which was sponsored by NIH. This was a 3-year, prospective, placebo-controlled, double-blind, multicenter study. Subjects were post-menopausal women, ages 45-64. Participants who had used HRT previously had to discontinue use at least 2 months prior to enrollment in this study. After a screening visit, eligible subjects were randomly assigned to receive one of five hormone replacement therapies (HRT) for up to 3 years of treatment. A total of 7 centers participated in the study. The treatment groups and sample sizes are listed in Table 2 below.

Table 2: Dosing Regimens for Treatment Groups (PEPI Study)

		CEE component		Progesterone component	
Treatment Group	n	Dose (mg/day)	Days of Cycle	Dose (mg/day)	Days of Cycle
CEE+MPA 2.5 mg cont.	120	0.625	1 - 28	MPA 2.5 mg	1 - 28
CEE+MPA 10 mg cyclic	118	0.625	1 - 28	MPA 10 mg Placebo	1 - 12 13 - 28
CEE only	119	0.625	1 - 28	Placebo	1 - 28
Placebo	119	Placebo	1 - 28	Placebo	1 - 28
CEE+MP 200 mg cyclic	120	0.625	1 - 28	MP 200 mg Placebo	1 - 12 13 - 28

The original goal of the PEPI study was to investigate the impact of progestins in combination with conjugated equine estrogens (CEE), on lipoproteins and other cardiovascular risk factors, including glucose, insulin, fibrinogen, and blood pressure. Endometrial biopsies were scheduled at baseline and at yearly visits for safety data, not efficacy data, in the original protocol. The results of these endometrial biopsies are now the focus of the analyses for the indication of prevention of endometrial hyperplasia in non-hysterectomized post-menopausal women who are receiving conjugated estrogen tablets. For this review, the Medical Officer selected the following efficacy variables:

The primary variable of interest is:

Incidence of endometrial hyperplasia at 36 months

Secondary variables of interest were:

Incidence of endometrial hyperplasia at 12 months

Incidence of endometrial hyperplasia at 24 months

The primary objective of this data analysis is the evaluation of the effect of MPA (as a component of combination estrogen-progestin HRT) on the prevention of endometrial hyperplasia in women with a uterus. The PEPI study enrolled post-menopausal women with or without a uterus, and used hysterectomy status in a stratified randomization process. The intent-to-treat (ITT) population for this submission is women with an intact uterus at the time of randomization. This is a subset of the total subjects in the study, but women with an intact uterus were balanced across the treatment groups, and make up 68% of the total randomized.

The only comparisons of interest for this NDA are each of the 2 the CEE+MPA treatment groups with the CEE-only treatment group. The results for the placebo group are included in the label to provide background information, but are not compared to any active-treatment group because the indication specifies that the intended patient population is women also receiving conjugated estrogens.

A total of 357 patients (with an intact uterus) were randomized to the 3 treatment groups of interest for this review. The three groups were similar with regard to the demographic characteristics at baseline, as shown in Table 3. Previous analysis by this reviewer of the other 2 treatment groups (Placebo and CEE+MP) in the PEPI study showed all 5 treatment groups in this study were similar on baseline characteristics.

Table 3: Demographic characteristics (PEPI Study)

	CEE + MPA 2.5 mg continuous (n=120)	CEE + MPA 10 mg cyclic (n=118)	CEE only (n=119)
	Mean (Std. Dev.) Range	Mean (Std. Dev.) Range	Mean (Std. Dev.) Range
Age (years)	56.7 (3.6)	55.9 (4.0)	56.3 (4.1)
Age at Menopause (years)	51.0 (2.7)	50.5 (3.1)	50.6 (3.3)
Duration of Menopause (years)	5.7 (2.7)	5.4 (2.9)	5.6 (2.6)
Weight (kg)	69.3 (11.1)	68.2 (12.3)	69.9 (12.8)
	n (%)	n (%)	n (%)
Race			
White	112 (93.3)	105 (89.0)	112 (94.1)
Black	3 (2.5)	5 (4.2)	3 (2.5)
Other	5 (4.2)	8 (6.8)	4 (3.4)

Source: PEPI data set

It was possible for subjects to temporarily drop from the study medication and continue in the study. It was also possible for subjects who missed a scheduled visit to continue participation in the study. Participation in the yearly study visits was similar for the 3 treatment groups of interest for this review (Table 4) and was also similar in the other 2 groups in the PEPI study. However, the number of subjects who had endometrial biopsies declined more over time for the CEE-only treatment group than for the CEE+MPA treatment groups (See Table 5). The reasons for discontinuing from the biopsy portion of the yearly visits are shown in Table 6.

Table 4: Subject participation in scheduled study visits (PEPI Study)

	CEE + MPA 2.5 mg continuous		CEE + MPA 10 mg cyclic		CEE only	
	n	% of rand.	n	% of rand.	n	% of rand.
Randomized	120	100.0 %	118	100.0 %	119	100.0 %
12 Month Visit	116	96.7 %	118	100.0 %	115	96.6 %
24 Month Visit	116	96.7 %	116	98.3 %	114	95.8 %
36 Month Visit	117	97.5 %	116	98.3 %	115	96.6 %

Source: PEPI data set

Table 5: Disposition of subjects at scheduled biopsy visits (PEPI Study)

	CEE+MPA 2.5 mg continuous		CEE+MPA 10 mg cyclic		CEE only	
	n	% of rand.	n	% of rand.	n	% of rand.
Initial Biopsy (Randomized)	**120**	**100%**	**118**	**100%**	**119**	**100%**
12 Month Visit:						
Discontinued from biopsy portion before 12-month visit; no further biopsies	4	3%	2	2%	6	5%
Missing 12 month biopsy	1	1%	0	0%	3	3%
Biopsy at 12 month visit	**115**	**96%**	**116**	**98%**	**110**	**92%**
24 Month Visit:						
Discontinued from biopsy portion before 24-month visit; no further biopsies	1	1%	3	3%	6	5%
Missing 24 month biopsy	4	3%	0	0%	3	3%
Biopsy at 24 month visit	**111**	**93%**	**113**	**96%**	**104**	**87%**
36 Month Visit:						
Discontinued from biopsy portion before 36-month visit; no further biopsies	6	5%	5	4%	9	8%
Biopsy at 36 month visit	**109**	**91%**	**108**	**92%**	**98**	**82%**

Source: PEPI data set

Table 6: Reasons for Discontinuation from Further Biopsies (PEPI Study)

	CEE+MPA 2.5 mg continuous		CEE+MPA 10 mg cyclic		CEE only	
	n	% of rand.	n	% of rand.	n	% of rand.
Discontinued from biopsy portion before 12-month visit	4	3%	2	2%	6	5%
Refused/No entry	1	1%	1	1%	3	3%
Missed Visit	3	3%	0	0%	2	2%
Hysterectomy	0	0%	1	1%	1	1%
Discontinued from biopsy portion before 24-month visit	1	1%	3	3%	6	5%
Refused/No entry	1	1%	1	1%	3	3%
Missed Visit	0	0%	1	1%	2	2%
Hysterectomy	0	0%	1	1%	1	1%
Discontinued from biopsy portion before 36-month visit	6	5%	5	4%	9	8%
Refused/No entry	5	4%	3	3%	4	3%
Missed Visit	1	1%	1	1%	2	2%
Hysterectomy	0	0%	1	1%	3	3%

Source: PEPI data set

Applicant's Analysis

The intent-to-treat (ITT) population for this submission is not the full PEPI study patient population. Only women who had an intact uterus at baseline are considered for the analyses for the indication of prevention of endometrial hyperplasia. The ITT population for this review is all women who had an intact uterus at the time of randomization to treatment. There were 120 such subjects in the CEE+MPA 2.5 mg continuous treatment group, 118 subjects in the CEE+MPA 10 mg cyclic treatment group, and 119 in the CEE-only treatment group.

In Section 3.3, the applicant reported only the 36-month results (primary time point) and did not discuss the results at 12 or 24 months (secondary time points) for the two CEE+MPA treatment groups. The applicant used separate Fisher's Exact tests to compare each of the two CEE+MPA treatment groups to the placebo group, and to compare the placebo group to the CEE-only treatment group, at 36-months. The applicant concluded that the incidence of endometrial hyperplasia in each of the CEE+MPA treatment groups was not significantly different from the placebo group, but that the incidence in the placebo group was significantly different from the CEE-only group.

The comparisons reported by the applicant are not the comparisons of interest for this NDA review. Specifically, to determine efficacy of either CEE+MPA treatment regimen for prevention of endometrial hyperplasia in women receiving estrogen treatment, a direct comparison to the CEE-only group is desired. The tests reported by the applicant do not provide sufficient evidence to make clear conclusions about the efficacy of the CEE+MPA treatments.

Table 7: Applicant's Results: Most Extreme Abnormal Result at 36 Months (ITT) (PEPI Study)

	CEE+MPA 2.5 mg continuous (n=120)		CEE+MPA 10 mg cyclic (n=118)		CEE only (n=119)		Placebo (n=119)	
	n	% of rand.	n	% of rand.	n	% of rand.	n	% of rand.
Total Number Hyperplasia Cases (% of rand.)	1	0.8	6	5.1	74	62.2	3	2.5
Type of Hyperplasia								
Adenocarcinoma	0	0.0	0	0.0	0	0.0	1	0.8
Atypical Hyperplasia	0	0.0	0	0.0	14	11.8	0	0.0
Complex Hyperplasia	0	0.0	2	1.7	27	22.7	1	0.8
Simple Hyperplasia	1	0.8	4	3.4	33	27.7	1	0.8

Source: Applicant's Tables 4 & 5 (Section 3.3)

Reviewer's Analysis

As noted in the previous section, the analyses reported by the applicant did not include the direct comparisons of the CEE+MPA treatment groups to the CEE-only treatment group. These are the desired comparisons for assessing efficacy for endometrial hyperplasia. Also, the applicant used Fisher's Exact tests, which do not adjust for centers in a multicenter study.

This reviewer reanalyzed the PEPI data, using the Cochran-Mantel-Haenszel (CMH) test to adjust for centers. The results are presented in Table 7 below. For the primary efficacy variable, incidence at 36 months, 2 hypothesis tests were done (CEE+MPA continuous vs. CEE-only; CEE+MPA cyclic vs. CEE-only). For the 2 secondary time points of interest, a total of 4 separate tests were done. After using a Bonferroni adjustment for multiple comparisons, all the tests showed a significant difference in the incidence of endometrial hyperplasia in favor of the CEE+MPA treatment regimens.

Table 8: Reviewer's Results (ITT) (PEPI Study)

	CEE+MPA 2.5 mg continuous		CEE+MPA 10 mg cyclic		CEE only	
	n	% of rand. (95% Conf. Intvl.)	n	% of rand. (95% Conf. Intvl.)	n	% of rand. (95% Conf. Intvl.)
Primary Variable						
Incidence of Hyperplasia through 36 months	1	0.8 * (-0.8, 2.4)	6	5.1 * (1.1, 9.1)	74	62.2 (53.5, 70.9)
Secondary Variable						
Incidence of Hyperplasia through 12 months	0	0.0 * (no CI possible)	4	3.4 * (0.1, 6.7)	43	36.1 (27.5, 44.7)
Incidence of Hyperplasia through 24 months	1	0.8 * (-0.8, 2.4)	5	4.2 * (0.6, 7.8)	60	50.4 (41.4, 59.4)

Source: PEPI data set

* All comparisons of CEE+MPA treatment groups to CEE-only treatment group showed a significant difference (p-value≤0.001) in incidence of endometrial hyperplasia.

It should be noted that the number of cases of endometrial hyperplasia per treatment group in the PEPI data set matched those reported by the applicant at the 36-month time point, but did not match the applicant's report for the CEE-only group at the 12-month or

24-month time points. In Section 3.3 of the applicant's report, Table 4 showed 25 cases at 12 months, and 54 cases at 24 months. The applicant's results were based solely on a literature review of published reports of the PEPI study. However, the applicant mentions that there are 30 cases in which the pathologists do not agree on the diagnosis.

The PEPI data set was submitted previously to the FDA by a different applicant, and was reviewed by this reviewer. In cases in which pathologists did not agree on a diagnosis, an arbitration process was used by the NIH to resolve the diagnosis. In discussions with the Medical Officer, it was agreed that the decision method for resolving the discrepancies which was used when the PEPI data set was submitted was satisfactory. Since we know how that data set was created, this reviewer decided to use the results from the PEPI data set.

Menopause Study Group (Woodruff Study)

Background

The Menopause Study Group is referred to as the Woodruff Study because Woodruff was the primary investigator. It was a 1-year, double-blind, randomized, multicenter trial. The patient population was post-menopausal women, ages 45-65, who had an intact uterus. Subjects were randomly assigned to receive one of five hormone replacement therapies (HRT) for up to 1 year of treatment. A total of 99 centers in the U.S. and Europe participated. The treatment groups are listed in Table 9 below. Endometrial biopsies were performed at 6 and 12 months after starting treatment.

Table 9: Dosing Regimens for Treatment Groups (Woodruff Study)

		CEE component		Progesterone component	
Treatment Group	n	Dose (mg/day)	Days of Cycle	Dose (mg/day)	Days of Cycle
CEE+MPA 2.5 mg cont.	345	0.625	1 - 28	MPA 2.5 mg	1 - 28
CEE+MPA 5.0 mg cont.	345	0.625	1 - 28	MPA 5.0 mg	1 - 28
CEE+MPA 5.0 mg cyclic	345	0.625	1 - 28	Placebo MPA 5.0 mg	1-14 15-28
CEE+MPA 10.0 mg cyclic	345	0.625	1 - 28	Placebo MPA 10.0 mg	1-14 15-28
CEE only	345	0.625	1 - 28	Placebo	1 - 28

The Medical Officer feels that the results of the Woodruff study should be considered only as supportive evidence because the study design did not meet our general requirements for an endometrial hyperplasia study. Specifically, there was only a two-week washout period prior to randomization; the method used in obtaining the endometrial biopsies was not consistent across centers with some centers using non-optimal methods; and some important biopsies were evaluated only by one pathologist, Dr. Woodruff.

The time point of interest for this study is the 12-month endometrial biopsy. Table 10 presents the incidence of endometrial hyperplasia by treatment group as reported by the applicant. The data was not available for reanalysis by this reviewer. As a supportive study, no comparisons between treatment groups were considered. This reviewer calculated 95% confidence intervals to provide further information for the Medical Officer's assessment.

Table 10: Applicant's Results (ITT) (Woodruff Study)

	CEE+MPA 2.5 mg contin.		CEE+MPA 5.0 mg contin.		CEE+MPA 5.0 mg cyclic		CEE+MPA 10.0 mg cyclic		CEE-only	
	n	% of rand. (CI)	n	% of rand. (CI)	n	% of rand. (CI)	n	% of rand. (CI)	n	% of rand. (CI)
Randomized	345		345		345		345		345	
Subjects with 12-month Biopsy	279		274		277		272		283	
Incidence of Hyperplasia through 12 months	2	0.6 (-0.2, 1.4)	0	0.0 (No CI)	3	0.9 (-0.1, 1.9)	0	0.0 (No CI)	57	16.5 (12.6, 20.4)

The incidence of endometrial hyperplasia at 12 months in the CEE-only treatment group of the Woodruff study (16.5%) was less than half the rate seen in the PEPI study at 12 months in the CEE-only group (36.1%). However, the Medical Officer feels the results of the both studies are consistent with her expectations based on additional sources.

APPEARS THIS WAY
ON ORIGINAL

Additional Analyses

The results of the placebo treatment group from the PEPI study were not considered in the efficacy analyses because no comparison of the active-treatment groups to placebo was desired. The Medical Officer decided that the label should include the information from the placebo group to provide background information on the incidence of endometrial hyperplasia in women with an intact uterus who are not receiving any HRT treatment. The results for the placebo group are given in Table 11.

Table 11: Reviewer's Results (Placebo Group; ITT) (PEPI Study)

	Placebo (n=119)		
Timepoint:	12 months	24 months	36 months
Total Number Hyperplasia Cases (% of rand.)	0 (0.0)	1 (0.8)	3 (2.5)
Type of Hyperplasia			
Adenocarcinoma	0	0	1
Atypical Hyperplasia	0	1	0
Complex Hyperplasia	0	0	1
Simple Hyperplasia	0	0	1

Source: PEPI data set

There was no placebo group in the Woodruff study.

APPEARS THIS WAY
ON ORIGINAL

Conclusions

The goal of the analyses for this NDA submission was to evaluate the effect of medroxyprogesterone acetate (MPA), as a component of combination estrogen-progestin HRT, on the prevention of endometrial hyperplasia in women with a uterus. The applicant has requested approval for only 2 of the doses reviewed in this application: MPA 5.0 mg/day cyclic, and MPA 10.0 mg/day cyclic. The continuous regimens were not submitted for approval.

The PEPI study included only one of the MPA cyclic regimens, the 10.0 mg/day dosage, with MPA taken during days 1-12 of each 28-day cycle. The estimated incidence rate for endometrial hyperplasia in this treatment group was 3.4% after 12 months on treatment, and 5.1% after up to 36 months on treatment. The results of the PEPI study indicate that there is a significantly lower incidence of endometrial hyperplasia in the CEE+MPA 10.0 mg/day cyclic treatment group than in the CEE-only treatment group.

The Woodruff study included both of the desired MPA cyclic regimens, with the MPA component being taken on days 15-28 of each 28-day cycle. The results showed an estimated 0.9% incidence of hyperplasia in the MPA 5.0 mg/day cyclic treatment group, and an estimated 0.0% incidence in the MPA 10.0 mg/day cyclic group, after 12 months on treatment. The estimated rate for the CEE-only treatment group in this study was 16.5% after 12 months. These results support the conclusion that MPA provides protection from endometrial hyperplasia in women with an intact uterus who are receiving CEE hormone replacement therapy.

The label which was submitted with this NDA does not include a Clinical Studies section. There are 2 general statements mentioning clinical data proposed in the Indications and Usage section, but no specifics about the studies or the results are given. This reviewer would like to have a Clinical Studies section added to the label which includes information on the study design, actual results, and statistical conclusions for both studies. Also, a table showing endometrial hyperplasia incidence rates for the CEE+MPA dose groups, CEE-only group, and placebo group, would be useful for easy reference.

/S/

Katherine B Meaker, M.S.
Mathematical Statistician

Concur: Dr. Nevius 7-6-98

Ms. Mele 7-7-98

cc:

Archival NDA 11-839
HFD-580
HFD-580/TvanderVlugt, LRarick
HFD-580/DMoore
HFD-715/ENevius, JMele, KMeaker, Division File, Chron

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 11839/S68

ADMINISTRATIVE DOCUMENTS

Group Leader Memorandum

JUL 23 1998

NDA:	11-839/S-068
Drug :	Medroxyprogesterone Acetate Tablets, USP - Provera® Tablets
Sponsor:	Pharmacia & Upjohn
Dosage/Strength:	5 mg and 10 mg tablets given orally
Proposed Indication:	Reduce the incidence of endometrial hyperplasia and endometrial carcinoma in nonhysterectomized postmenopausal women
NDA Submitted:	July 31, 1997
NDA Received:	August 4, 1997
NDA Completed:	July 31, 1997
Date of Memorandum:	July 23, 1997

Background

Provera® (medroxyprogesterone acetate) has been marketed since 1960 and is currently approved in 2.5, 5, and 10 mg strengths for the treatment of secondary amenorrhea and abnormal uterine bleeding due to hormone imbalance in the absence of organic pathology, such as fibroids or uterine cancer.

In April of 1986, the agency received an efficacy supplement providing for the use of cyclic Provera® to oppose the endometrial effects of estrogen in menopausal women with uteri receiving estrogen therapy. This application was not approved, with the primary concern that the literature provided did not provide adequate evidence of efficacy for this indication. On July 31, 1997, the sponsor submitted again an efficacy supplement for the indication of reduced endometrial hyperplasia in nonhysterectomized postmenopausal women. There were two major studies performed during this interim period, the NIH-sponsored PEPI trial (Postemenopausal Estrogen/Progesterone Interventions) and the MSG trial (Menopause Study Group). These two trials form the basis for this application.

Desired Indication: Provera tablets are indicated to reduce the incidence of endometrial hyperplasia and endometrial carcinoma in nonhysterectomized postmenopausal women receiving estrogen replacement therapy."

Desired Dose: "Provera may be given in dosages of 5 to 10 mg daily for 12 to 14 consecutive days per month, either beginning on the 1st day of the cycle or on the 16th day of the cycle."

Trial Results

The PEPI trial was a 3 year, prospective, double-blind, placebo controlled trial of 875 women (596 with a uterus, 279 without a uterus) assigned to one of five treatment groups:

Arm 1	**Premarin 0.625 mg daily**	**plus**	**Placebo**
Arm 2	**Premarin 0.625 mg daily**	**plus**	**Provera 10 mg days 1-12/Placebo days 13-28**
Arm 3	Premarin 0.625 mg daily	plus	Provera 2.5 mg daily
Arm 4	Premarin 0.625 mg daily	plus	Micronized progesterone @ 200 mg days 1-12
Arm 5	**Placebo**	**plus**	**Placebo**

The treatment arms which are relevant to the sponsor's desired indication involve the results in arms 1 (n=119), 2 (n=119) and 5 (n=120).

Results revealed hyperplasia rates of 62% in Arm 1 (estrogen only), compared to 5% in arm 2 (Premarin plus 10 mg Provera given cyclically), and 3% in arm 5 (placebo only). Thus, this trial clearly supports that Provera 10 mg given in a cyclic regimen with estrogen reduces the incidence of hyperplasia to rates which were comparable to placebo. Of note, only one patient (in the placebo arm) was diagnosed with endometrial adenocarcinoma during the study. Provera was well tolerated during this 3 year trial, and the adverse events noted were no different in nature than those already noted in the product's label.

The MSG was a 1 year, prospective, double-blind, placebo-controlled trial of 1724 postmenopausal women assigned to one of five treatment groups:

Arm 1	Premarin 0.625 mg daily	plus	Provera 2.5 mg daily
Arm 2	Premarin 0.625 mg daily	plus	Provera 5 mg daily
Arm 3	**Premarin 0.625 mg daily**	**plus**	**Placebo days 1-14 then Provera 5 mg days 15-28**
Arm 4	**Premarin 0.625 mg daily**	**plus**	**Placebo days 1-14 then Provera 10 mg days 15-28**
Arm 5	**Premarin 0.625 mg daily**	**plus**	**Placebo days 1-28**

The treatment arms which are relevant to the sponsor's desired indication involve the results in arms 3 (n=277), 4 (n=272) and 5 (n=283).

Results revealed hyperplasia rates at one year of 1% in arm 3, 0% in arm 4 compared to a rate of 20% in arm 5 (premarin only control arm). This trial supports that Provera 5 and

10 mg given in a cyclical fashion prevents endometrial hyperplasia. Only two patients developed endometrial cancer at one year: one patient from arm 4 and one from arm 5. Provera was again well tolerated during this one year trial, and the adverse events noted were no different in nature than those already noted in the product's label.

Conclusion: The PEPI trial supports the approval of 10 mg Provera given cyclically on days 1-12 for the prevention of endometrial hyperplasia. The MSG trial supports the approval of 5 and 10 mg Provera given cyclically on days 15-28 for the prevention of endometrial hyperplasia. There is no evidence from either the PEPI or MSG trials that endometrial carcinoma, per se, was prevented by Provera. Additionally, while the sponsor desires a labeling indication for "nonhysterectomized postmenopausal women receiving estrogen replacement therapy," their studies involved on conjugated equine estrogen therapy. In conclusion, therefore, this application supports the safety and efficacy of Provera 5 and 10 mg administered on a cyclical basis to prevent endometrial hyperplasia in postmenopausal women receiving conjugated estrogen replacement therapy.

/S/

Marianne Mann, M.D.
Deputy Director, HFD-580

cc:
HFD-580/Rarick, VanderVlugt
NDA 11-839/S-068

MEMORANDUM

10/3/97

From: Robert H. Seevers, Reviewing Chemist

To: Division file on NDA 11-839

10/3/97

Through: Moo-Jhong Rhee, Chemistry Team Leader

Re: NDA 11-839 Supplement SE1-068

Date: October 3, 1997

The submission is an efficacy supplement for an additional indication for the drug product. The new indication is for the use of the drug product for 12-14 days a month in combination with continuous estrogen replacement for the prevention of estrogen induced endometrial hyperplasia and endometrial carcinoma. The sponsor has submitted request for a categorical exclusion for an environmental assessment per 21 CFR § 25.15 (d) dated September 2, 1997 (CDER date September 4, 1997).

The firm states that, although action on this supplement will increase the use of the active moiety, the expected introduction concentration (EIC) will be less than 1 part per billion (ppb) and further, that no extraordinary circumstances, as specified in 21 CFR § 25.21, exist to its knowledge.

The categorical exclusion (for EA) may be granted. Supplement SE1-068 may approved from a chemistry standpoint.

Item 13. Patent Information

U.S. Patent 3,777,364 which claimed medroxyprogesterone acetate expired in 1985.

Item 14. Patent Certification

Cyclical use of medroxyprogesterone acetate for 12-14 days each month in combination with daily administration of oral estrogen replacement therapy in postmenopausal women does not infringe on any unexpired U.S. patents.

Item 15. Debarment Statement

Not applicable. None of the studies were conducted by Pharmacia & Upjohn.

EXCLUSIVITY SUMMARY FOR NDA # 11-839 SUPPL # 068 AUG - 4 1998

Trade Name Provera® Generic Name (medroxyprogesterone acetate) tablets

Applicant Name Pharmacia & Upjohn HFD # 580 CSO: Markow

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 /X/

b) Is it an effectiveness supplement?

YES /X/ NO / /

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

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 /X/ 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 /__/ NO /_X_/

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

_____

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?

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# 11-839 Medroxyprogesterone acetate

NDA# 89-386 Medroxyprogesterone acetate

NDA# 83-242 Medroxyprogesterone acetate

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 /X/ 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 /X_/

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:

_____

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.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /__/	NO /X_/
Investigation #2	YES /__/	NO /X/
Investigation #3	YES /__/	NO /__/
Investigation #4	YES /__/	NO /__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /_/	NO /X/
Investigation #2	YES /_/	NO /X/
Investigation #3	YES /_/	NO /__/
Investigation #4	YES /_/	NO /__/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

1. The postmenopausal estrogen/progestin interventions (PEPI) trial: rationale, design and conduct
2. Woodruff JD, Pickar JH. Incidence of endometrial hyperplasia in postmenopausal women taking conjugated estrogens (Premarin) with medroxyprogesterone acetate or conjugated estrogens alone (The Menopause Study Group).

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 /__/ ! NO /X / Explain: This is a literature reference

Investigation #2

IND #_____ YES /_/ ! NO /X_/ Explain: This is a literature reference

Investigation #3

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

Investigation #4

IND #_____ YES /_/ ! 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 /X_/ Explain: Provided ! NO /___/ Explain _____

in cover letter and additional !

support by references. !

Investigation #2

YES /X/ Explain Provided ! NO /___/ Explain _____

in cover letter and additional !

support by references. !

(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 / X / NO / /

If yes, explain: These two studies were independent published trials not conducted by this sponsor.

/S/

Signature

8/4/98

Date

Title: Consumer Safety Officer

/S/

Signature of Office/
Division Director

8/4/98

Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the ıe of the last action.

NDAs: 11-839/S-068 Circle one: SE1
HFD 580 Trade and generic names/dosage form: Provera® (medroxyprogesterone acetate) tablet
Action: AP AE NA

Applicant: Pharmacia & Upjohn, Inc. Therapeutic Class 3S

Indication(s) previously approved: Secondary amenorrhea; abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer.
Pediatric information in labeling of approved indication(s) is NOT APPLICABLE.

Proposed indication in this application is for the use of Provera® foe 12-14 days each month in combination therapy with continuous estrogen replacement therapy for prevention of estrogen induced endometrial hyperplasia and endometrial carcinoma in nonhysterectomized post-menopausal women.

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.
IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)
WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- ___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- ___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- ___ c. The applicant has committed to doing such studies as will be required.
  - ___ (1) Studies are ongoing,
  - ___ (2) Protocols were submitted and approved.
  - ___ (3) Protocols were submitted and are under review.
  - ___ (4) If no protocol has been submitted, attach memo describing status of discussions.
- ___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes _X_ No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.
This page was completed based on information from the Medical Reviewer.

/S/ Project Manager — 7/31/98
Signature of Preparer and Title — Date

cc: Orig NDA19-726
HFD-580/Div File
NDA/Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

NDA 11-839/S-068
Provera® (medroxyprogesterone acetate) Tablets

Division Director's Memo

This application will be signed off at the Division level. No memo is necessary.

NDA 11-839/S-068
Provera® (medroxyprogesterone acetate) Tablets

Safety Update Review

Included in Medical Officer reviewdated_____.

NDA 11-839/S-068
Provera® (medroxyprogesterone acetate) Tablets

EER

There were no manufacturing changes - no EER is required.

NDA 20-870
Combipatch™ (estradiol/norethindrone acetate)

Pharmacology Review

This application is a supplement based on existing literature. No pharmacology review is necessary.

NDA 11-839/S-068
Provera® (medroxyprogesterone acetate) Tablets

Microbiology Review

No microbiology review is required.

NDA 11-839/S-068
Provera® (medroxyprogesterone acetate) Tablets

Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

NDA 11-839/S-068
Provera® (medroxyprogesterone acetate) Tablets

Federal Register Notices

This application was not the subject of any Federal Register Notices.

NDA 11-839/S-068
Provera® (medroxyprogesterone acetate) Tablets

Advertising Material

No advertising material has been submitted.

NDA 11-839/S-068
Provera® (medroxyprogesterone acetate) Tablets

DSI Audit of Clinical Studies

No clinical audits were necessary as determined in the filing meeting held September 8, 1997.

R (ARKOW

MEETING MINUTES

Meeting Date: September 16, 1997
Time: 1:00 p.m.- 2:00 p.m.
Location: Parklawn 17B-43

Application: NDA 11-839/S-068

Type of Meeting: Teleconference (616) 833-0527

Sponsor: Pharmacia & Upjohn

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

Meeting Recorder: John C. Markow, R.Ph., J.D. - Consumer Safety Officer, DRUDP, (HFD-580)

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)
Theresa van der Vlugt, M.D. - Medical Officer, DRUDP (HFD-580)
K. Gary Barnette, Ph.D. - Pharmacokinetics Reviewer, DPE II @ DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Lana L. Pauls, M.P.H. - Chief, Project Management Staff, DRUDP (HFD-580)
John C. Markow, R.Ph., J.D. - Consumer Safety Officer, DRUDP, (HFD-580)

External Constituent Attendees:

Donald R. Gieseker, Pharm. D. - Regulatory Associate Director, Regulatory Affairs
Lynn Wathen, Ph.D. - Clinical Monitor
Sue Cammarata, M.D. - Clinical Monitor
Roger Garceau, M.D. - Director Medical Women's Health
Henk DekoningGans, M.D. - Vice President, Female Health Products
Michael J. Schoenfeld - Clinical Trials Specialist
Rick Davison - CMC Specialist
Mike Burdick - Regulatory Affairs
Nancy Busso - Regulatory Affairs
Mohamed Rahimy - Pharmacokineticist
Dennis Stalker, Ph.D. - Pharmacokineticist

Background:

This application was submitted July 31, 1997, and received August 4, 1997. This application was submitted as an Efficacy Supplement to support a new supplemental indication for the drug Provera® for 12-14 days each month in combination with continuous estrogen replacement for prevention of estrogen-induced endometrial hyperplasia and endometrial carcinoma in nonhysterectomized post-menopausal women.

Meeting Objectives:

1. To discuss any noted review issues that may effect the review process.

Discussion Points:

- Clinical
  - the proposed labeling should reflect the use of Provera® with Premarin® 0.625mg instead of "estrogen replacement regimen"
  - whether Provera® bioequeivalent to the medroxyprogesterone acetate used in the published submitted trials
  - Provera® used in the PEPI trial, Cycrin® used in the Menopausal Study Group Trial; Cycrin® and Provera® are AB-rated
  - why is sponsor not asking for continuous use
  - potential process patent infringement will prevent such broadening
- Chemistry
  - which manufacturing process will be used;

Decisions reached:

- sponsor will provide feedback to the Agency on the labeling issue (use of "estrogen replacement regimen" instead of Premarin®) after further investigation
- sponsor verified that the will be used and that they have no immediate plans to change the process

Action Items:

Item	Responsible Person	Due Date
1. Feedback on labeling question	Don. Gieseker	Within review period

/S/ 9/8/97
Minutes Preparer:

/S/ 9/25/97
Chair Concurrence:

cc: Original NDA 11-839/S068
HFD-580/Div. Files
HFD-580/JMarkow/wpfiles/nda/tcons/11839tc2.min
HFD-580/L Rarick/TvanderVlugt/MRhee/GBarnette/LPauls

Concorrences: LRarick 9.25.97/TvanderVlugt 9.23.97/GBarnette 9.23.97/MRhee 9.22.97/LPauls 9.19.97

MEETING MINUTES

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 11839/S68

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 11-839/S-068

AUG 18 1997

Pharmacia & UpJohn
700 Portage Road
Kalamazoo, MI 4900

Attention: Donald R. Gieseker, Pharm D.
Associate Director, Regulatory Affairs

Dear Mr. Gieseker:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Provera Tablets
NDA Number:	11-839
Supplement Number:	S-068
Date of Supplement:	July 31, 1997
Date of Receipt:	August 4, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on October 3, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely, /S/

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ORIGINAL

Pharmacia & Upjohn

Office of:
Donald R. Gieseker, Pharm.D.
Associate Director
U.S. Regulatory Affairs

Telephone No. (616) 833-8527
Facsimile No. (616) 833-8237

NDA SUPP AMEND
SE1-068 BC

January 8, 1998

AJ 2/2/98

CENTER FOR DRUG
REC'D
JAN 0 9 1998
HFD-580
EVALUATION AND RESEARCH

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 11-839, S-068
PROVERA® Tablets

Amendment 001

Dear Dr. Rarick:

During a teleconference, held between the Division of Reproductive and Urologic Drug Products, and Pharmacia and Upjohn on September 16, 1997 concerning the above referenced efficacy supplement to NDA 11,835, the FDA noted that based on a review of the data at that time it appeared that the data would only support the sequential use of Provera® to suppress endometrial hyperplasia and carcinoma induced by Premarin® (conjugated estrogens). During the teleconference, Pharmacia and Upjohn asked to provide an argument for retaining the proposed claim to "estrogens" at a later date which was acceptable to the division.

Enclosed are the arguments in support of use with estrogens. The primary argument centers on the general ability of all estrogen substances to induce endometrial hyperplasia and carcinoma and that progestins as a class, to which Provera® belongs, have the ability to suppress the hyperplasia.

If you have any questions regarding this submission, please contact Donald R. Gieseker at (616) 833-8527. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

D. Gieseker

Donald R. Gieseker, Pharm.D.
Associate Director
U.S. Regulatory Affairs

DRG:crdt
Attachments

cc: J. Markow, R.Ph., J.D., FDA Project Manager

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
2/2/98
CSO INITIALS DATE

NJ
RHS
2/1/98

Efficacy Supplement
Review Pending
J.W. van der Vlugt
1/21/98

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

ORIGINAL

Pharmacia & Upjohn

NDA SUPP AMEND
SE1-068 BL

Office of:
Donald R. Gieseker, Pharm.D.
Associate Director
Regulatory Affairs

Telephone No. (616) 833-8527
Facsimile No. (616) 833-8237

July 22, 1998

Lisa Rarick, M.D., Director
Division of Urologic and Reproductive Drug Products HFD 580
Center for Drug Evaluation and Research
Food and Drug Adminsitration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 11-839 (Supplement July 31, 1997)
PROVERA® Tablets
(medroxyprogesterone acetate tablets)

Amendment 02

Dear Dr. Rarick:

Enclosed are changes to the proposed package insert for the above referenced NDA supplement both as a paper version and as a WORD document. These changes were previously sent by FAX on July 21 to Randy Olmstead. The disk has been virus checked.

If you have any questions regarding this submission, please contact Donald R. Gieseker at (616) 833-8527. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Donald R. Gieseker, Pharm.D.
Associate Director
Regulatory Affairs

DRG:crdt
Attachments

cc: Randy Olmstead, FDA Project Manager
John Markow, FDA Project Manager

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 23 1998
HFD-580

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I ☐ MEMO

CSO INITIALS DATE

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000