CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-843

ADMINISTRATIVE DOCUMENTS

NDA 20-843
Prometrium (progesterone, USP) Capsules
Schering-Plough Research Institute

Division Director's Memo

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

Group Leader Memorandum

NDA:	20-843
Drug :	Prometrium® Progesterone
Sponsor:	Schering-Plough Research Institute
Dose Formulation:	100 mg capsules
Doses Proposed:	2 capsules (200 mg) taken once daily for the first 12 days of each 28 day cycle in non-hysterectomized women who are taking conjugated estrogen tablets daily
Proposed Indication:	Endometrial Protection
NDA Submitted: NDA Received: Review Completed:	3/10/97 3/11/97 12/14/98

Background

The sponsor submitted this NDA for Prometrium®. The indication is for the prevention of endometrial hyperplasia in non-hysterectomized women who are receiving daily therapy with conjugated estrogen tablets. In support of this indication, the sponsor analyzed data from PEPI (the Postmenopausal Estrogen/Progestins Interventions Trial).

Trial Results

The data from the PEPI trial supported the efficacy of 200 mg micronized progesterone (MP), or Prometrium®, taken once daily for the first 12 days of each 28-day cycle in combination with conjugated estrogen 0.625 mg daily for the prevention of endometrial hyperplasia. The trial was 36 months in duration and enrolled a total of 596 women with a uterus. Patients were randomized to one of five treatment regimens, of which three were relevant to this NDA:

Placebo:	n=119
Conjugated estrogen alone:	n=119
Conjugated estrogen plus MP 200 mg taken cyclically:	n=120

Trial results revealed that endometrial hyperplasia occurred in 62% of patients receiving CEE alone versus 5% of patients receiving cyclical treatment with MP and 3% of patients receiving placebo. Thus, the addition of MP to CEE therapy

for at least 10 days/cycle effectively reduced the rate of endometrial hyperplasia seen with CEE alone.

Conclusions

I agree with the primary medical reviewer that this NDA be approved.

/S/ M.D.

Marianne Mann, M.D. 12/15/98
Deputy Director, HFD-580

MEMORANDUM

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

DATE: March 5, 1998

FROM: Diane Moore
Division of Reproductive and Urologic Drug Products (HFD-580)
FAX; (301) 827-4267

SUBJECT: Pediatric labeling for Prometrium NDA 20-843

TO: File

This drug is indicated for post-menopausal women who are receiving conjugated estrogens tablets. It is not appropriate for use in children of any age. Therefore, pediatric studies are not needed.

/S/

Signature

NDA 20-843
Prometrium (progesterone, USP) Capsules
Schering-Plough Research Institute

Safety Update Review

The safety update is included in Medical Officer review dated February 25, 1998.

NDA 20-843
Prometrium (progesterone, USP) Capsules
Schering-Plough Research Institute

Microbiology Review

No microbiology review is required for oral capsules.

NDA 20-843
Prometrium (progesterone, USP) Capsules
Schering-Plough Research Institute

Advisory Committee Meeting Minutes

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

NDA 20-843
Prometrium (progesterone, USP) Capsules
Schering-Plough Research Institute

Federal Register Notices

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

NDA 20-843
Prometrium (progesterone, USP) Capsules
Schering-Plough Research Institute

Advertising Material

No advertising material has been submitted.

13. PATENT INFORMATION

Please reference our February 8, 1996 submission to our NDA 19-781 (PROMETRIUM Capsules), pages 1 of Section 13, Volume 2.2. There are no changes to the patent information.

PATENT INFORMATION

U.S. patents pertaining to the drug progesterone: None.

U.S. patents pertaining to the composition and formulation of PROMETRIUM (progesterone, USP) Capsules: None.

U.S. patents pertaining to methods of use of PROMETRIUM (progesterone, USP) Capsules: None.

The person signing this application on behalf of the applicant declares that he is aware of no U.S. patent which claims the drug progesterone, the PROMETRIUM (progesterone, USP) Capsules, or a method of using the PROMETRIUM (progesterone, USP) Capsules, and with respect to which U.S. patents a claim of patent infringement could reasonably be asserted against a person, not licensed thereunder by the owner, who engages in the manufacture, use or sale of the PROMETRIUM (progesterone, USP) Capsules.

EXCLUSIVITY SUMMARY for NDA # _20-843_____ SUPPL #_____

Trade Name __Prometrium____ Generic Name __(progesterone, USP) Capsules

Applicant Name _Schering-Plough Research Institute__ HFD-580_____

Approval Date, if known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES /_X__/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X__/

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

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

YES /_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 /_X__/ NO /___/

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

__3 _____

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

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

YES /___/ NO /_X__/ OTC Switch /___/

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# _19-781 _____ __Prometrium_____

NDA# _20-701_____ ___Crinone_____

NDA# _20-756_____ __Crinone_____

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 /_X_/ 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:

_____

YES /___/ NO /___/

(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 /_X_/ 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:

Study H89-117 (efficacy) (IND

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

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

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 /____/

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

---

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 /_X__/ NO /__/
Investigation #2 YES /___/ NO /___/

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

__Study H89-117 (IND __NDA 11-839 Provera_____

__(data from a different study arm of the same study was used to approve an efficacy supplement for Provera)

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"):

_____ _____

_____ _____

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 # Study H89-117 YES /___/ ! NO /_X__/ Explain: _NIH study under individual investigator with three sponsors supporting the study_____

Investigation #2

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 _____	NO /___/ Explain _____
The predessor, La Salle, and Schering provided support for the study_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

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

YES /___/ NO /_X_/

If yes, explain: _____

/S/ 11/20/98

Signature Date

_Diane Moore_____
Name (type or print)

_Project Manager_____
Title

/S/ 11/23/98

Signature of Division Director Date

__Dr. Lisa Rarick_____
Name (type or print)

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

19. CLAIMED EXCLUSIVITY

Pursuant to the provisions of Section 505(c)(4)(D)(iii) and 505(j)(4)(D)(iii) of the Food, Drug and Cosmetic Act (FDCA) and 21 C.F.R. Section 314.108(b)(4), in the February 8, 1996 submission to NDA 19-781, the applicant has claimed three (3) years of exclusivity for its PROMETRIUM (progesterone, USP) Capsules for oral administration attaching to the dosage form and route of administration and extending to any use of micronized progesterone capsules for oral administration.

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 time of the last action.

/BLA #_NDA 20-843_____ Supplement # _____Circle one: SE1 SE2 SE3 SE4 SE6

HFD-580_ Trade and generic names/dosage form: _Prometrium_(progesterone, USP) Capsules___Action: AP (AE) NA

Applicant _Schering-Plough Research Institute__ Therapeutic Class_____3S_____

Indication(s) previously approved __none_____
Pediatric information in labeling of approved indication(s) is adequate _X_ inadequate __
Proposed indication in this application___Prevention of endometrial hyperplasia_____

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTINS 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-1 month) __ Infants (1month-2yrs) __Children (2-12yrs) ___ Adolescents (12-16 yrs)

___ 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.

_X_ 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? _X_ Yes ___ No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from _____ (e.g., medical review, medical officer, team leader)

/S/ 11/16/98

Signature Of Preparer And Title Date

CC: ORIG NDA/BLA # NDA 20-843__
HFD-580/DIV FILE
NDA/BLA ACTION PACKAGE
HFD-006/ KROBERTS

(revised 10/20/97)

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

Department of
Public Health Sciences
Telephone: (910) 716-2498
Fax: (910) 716-5425

MEMORANDUM

PEPI COORDINATING CENTER

TO: Lisa Rarick, MD

FROM: June Pierce JP

DATE: June 20, 1997

SUBJECT: PEPI Clinical Centers

Dear Dr Rarick,

The following information is being supplied in response to a request for information regarding the clinical centers involved with The Postmenopausal Estrogen/Progestin Interventions Trial. There were seven clinical centers and were coded from 1 to 8 (7 was skipped) under the variable named "cccode".

cccode	Clinical Center	Principal Investigator
1	The University of California, San Diego	Elizabeth Barrett-Connor, MD
2	The Johns Hopkins University, Baltimore	Trudy L Bush, PhD
3	The University of California, Los Angeles	Howard Judd, MD
4	George Washington University, Washington, DC	Valery T Miller, MD
5	The University of Texas Health Sciences Center, San Antonio	José Trabal, MD
6	The University of Iowa, Ames	Helmut Schrott, MD
8	Stanford University, California	Marcia Stefanick, PhD

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: December 31, 1999
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
NHLBI WITH NICHD, NIDDK, NIAMS, NIA

2. DATE OF SUBMISSION
June 24, 1997

3. ADDRESS *(Number, Street, City, State and Zip Code)*
Two Rockledge Centre
6701 Rockledge Dr
Bethesda, MD 20892

4. TELEPHONE NUMBER *(Include Area Code)*
(301) 435-0555

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Micronized Progesterone Capsules

6. IND NUMBER *(If previously assigned)*

7. INDICATION(S) *(Covered by this submission)*
Hormone Replacement Therapy

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION

N/A

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
— — —

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☒ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☐ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☒ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Paula Einhorn, MD; PEPI Project Officer

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Joseph Kelaghan, MD; NICHD Liaison to PEPI

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Joseph Kelaghan, MD	Joseph Kelaghan	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
NICHD 9000 Rockville Pike Bethesda, MD 20892	(301) 496-4924	6/24/97

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001)

MEMORANDUM

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

DATE: December 10, 1998

FROM: Diane Moore
Division of Reproductive and Urologic Drug Products (HFD-580)
FAX: (301) 827-4267

SUBJECT: NDA 20-743 Statistical Labeling Revisions

TO: Ms. Rachael Steiner
Regulatory Affairs Associate
Schering-Plow Research Institute

Please ask your statistician to look at the patient records for the following three patients in the data set used to create the graph in figure 1:

Group	Patient. ID	Time to first event	Type of Hyperplasia
Placebo		726 days	Atypical
Placebo		1055 days	Simple
Placebo		1071 days	Complex

Our statistician will gladly speak with your statistician about how these numbers were calculated. Also, the denominator for the placebo group (women with intact uteri at the start of the study who did not drop out or have previous hyperplasia) at 24-months should not be n-289.

/S/

Diane Moore, Project Manager
Division of Reproductive and Urologic
Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/Tvan der Vlugt/LKammerman/KMeaker/DMoore

INFORMATION REQUEST

MEMORANDUM

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

DATE: November 13, 1998

FROM: Diane Moore
Division of Reproductive and Urologic Drug Products (HFD-580)
Phone (301) 827-4260
FAX (301) 827-4267

SUBJECT: Revised Prometrium Labeling for Carcinogenesis, Mutagenesis, Impairment of Fertility section

TO: Tonja Johnson
Schering Corporation

Please replace the Carcinogenesis section with the following section:

Carcinogenesis, Mutagenesis, Impairment of Fertility section

Progesterone has not been tested for carcinogenicity in animals by the oral route of administration. When implanted into female mice, progesterone produced mammary carcinomas, ovarian granulosa cell tumors and endometrial stromal sarcomas (1). In dogs, long term intramuscular injections produced nodular hyperplasia and benign and malignant mammary tumors (2). Subcutaneous or intramuscular injections of progesterone decreased the latency period and increased the incidence of mammary tumors in rats previously treated with a chemical carcinogen (3).

Progesterone did not show evidence of genotoxicity in in vitro studies for point mutations or for chromosomal damage. In vivo studies for chromosome damage have yielded positive results. Exogenously administered progesterone has been shown to inhibit ovulation in a number of species and it is expected that high doses given for an extended duration would impair fertility until the cessation of treatment.

(1) International Agency for Research on Cancer (IARC) V.6, 1974; IARC V. 21, 1979
(2) K.S. Larrson and D. Machin, Safety requirements for contraceptive steroids. F. Michal (ed). Cambridge University Press, Cambridge. pp. 30-269, 1989.
(3) Sixth Annual Report on Carcinogens V. 2, pp 693-696, 1991.

/S/

Signature

Moore

MEETING MINUTES

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

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

External Participant: none

Type of Meeting: Labeling

Meeting Chair: Dr. Lisa Rarick

Meeting Recorder: Mrs. Diane Moore

FDA Attendees:

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

Meeting Objective:

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

Discussion Points:

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

- Clinical Pharmacology
  - under the **Pharmacokinetics** section, **Absorption** subsection, the relative bioavailability statement is wrong because of the way the study was performed; the Approvable letter for NDA 19-781 requested the section be removed
- Statistics
  - the information requested November 11, 1997, concerning the criteria used by the local rater for a final diagnosis of biopsy specimens has not been received
  - the data in the pharmacokinetic section is based on a 75% Caucasian population

Decisions reached:

[redacted]

- General
  - this label should incorporate changes from the secondary amenorrhea label; sections in the label should be separated according to the indications of secondary amenorrhea and endometrial protection
  - the black box containing the warning against the use of progestational agents during the first four months of pregnancy should be removed
  - the tables in the label should be numbered
  - labeling comments should incorporate comments from the proposed Biopharmaceutics drug interaction study
- Chemistry
  - **DESCRIPTION** section
    - the quality of the inactive ingredients; peanut oil, gelatin, glycerin and lecithin should be shown using USP or NF ratings
  - **HOW SUPPLIED** section
    - the term "Prometrium 100 mg Capsules" should be revised to read
- Statistics
  - the label should indicate that the lower dose for secondary amenorrhea was not effective; the results for all groups should be included
- Clinical Pharmacology
  - under the **Pharmacokinetics** section, **Absorption** subsection, in the second sentence that begins, the phrase that reads, should be deleted
  - Special Populations
    - the profile of the target population should be in the label
- **Clinical Studies** section
  - the two indications, secondary amenorrhea and endometrial protection, should be separated in the label in the different sections; the Endometrial Protection indication should be listed first; the second title should be Secondary Amenorrhea; the title of the indication should precede the appropriate paragraphs.
  - the label should report results from all three dose groups (200 mg, 300 mg and placebo) and indicate which other dose groups are less effective; the numbers must add up to 107
  - in the sentence that begins, the phrase, should be replaced by
  - the second Endometrial Protection paragraph that begins, a sentence should be inserted before this sentence that reads,

- the demographics of the study should be described
- in the title for the table that begins,

  - another approach is to include a Kaplan Meier Survival Graph with the most extreme results; hyperplasia rates should be reported at 1, 2, and 3 years; numbers should be included; the sponsor will be asked to submit this for review regarding its interpretability
  - the table should include a breakdown of who discontinued and for what reasons at the 36 month visit and the type of hyperplasia found
  - the demographics should be described
- the following table entitled,

  should be deleted; the pertinent positives should be summarized under the **ADVERSE REACTIONS** section

- **CONTRAINDICATIONS** section
  - item number 8 should be moved to item number 1 and placed in bold face type; the other items should be renumbered accordingly
- **WARNINGS** section
  - in item number 4, the phrase, should be deleted
- **PRECAUTIONS** section
  - in item number 6 that begins, should be revised to read,
  - item number 7 that begins, should be deleted
  - in item number 9 that begins, should be deleted
  - item number 11 should be deleted; the information is covered in the indications section

Physician description of information for the Patient

- General
  - the entire phrase,

    should be placed in bold face type
- **CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY** section
  - in the first paragraph, third sentence that begins, should be deleted; it is not supported by the data
  - the fourth and fifth paragraphs should be reviewed by the Pharmacology/Toxicity reviewer
- **Pregnancy Category X**
  - the sentence that begins, should be revised to read,
- **Nursing Mothers**
  - the first sentence that begins, should be deleted
- **Pediatric Use**
  - in the sentence that begins, the word should be replaced by the word

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

Patient Insert

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

Action Items:

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

Action Items:

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

Studies section of labeling

- check the phrase "tight and light" in in the third sentence that begins, "Dispense in tight . . .," in the HOW SUPPLIED section with Chemist — Mrs. Moore — one week

/S/ 2/12/98
Signature, minutes preparer

/S/ 2/16/98 for HJolson
Concurrence, Chair

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

drafted: dm/1.18.98/n20843sm.113

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

Concurrence:
LPauls, AMitra 01.23.98/KMeaker 01.26.98/Tvan der Vlugt, LStockbridge 01.27.98
HJolson 01.28.98/SSlaughter 01.29.98/LKammerman 02.03.98/SHaidar, GBarnette 02.12.98

MINUTES of TELECON

Date: January 16, 1998 **Time:** 3:42 - 4:00 PM **Location:** Parklawn; Mrs. Moore's Office

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

External Participant: Schering

Type of Meeting: Chemistry Guidance

Meeting Chair: Dr. Amit Mitra

Meeting Recorder: Mrs. Diane Moore

FDA Attendees:

Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

External Constituents:

Paula E. Rinaldi - Manager, Regulatory Affairs
Denise Flannigan, Ph.D. - Manager, World Wide Regulatory Affairs, Technical Support

Meeting Objective:

To discuss the categorical exclusion request for Prometrium (NDA 20-843).

Discussion Points:

- in November, 1995, Schering had submitted an abbreviated environmental assessment (EA) to the NDA
- the guidance was changed in July 1997, so that if the environmental introduction calculation (EIC) is below one part per billion, the sponsor can request a waiver for a categorical exclusion from the environmental assessment
- the calculations for the environmental assessment for this product are in volume 1.2, section 43A, page 15

Decisions reached:

- the sponsor should refer to the calculations in the NDA for environmental impact and CFR 25.3 when requesting a waiver for the environmental assessment

Action Items:

Item:	Responsible Person:	Due Date:
• submit a request for waiver for environmental assessment	Schering	one week

/S/ 2/3/98
Signature, minutes preparer

/S/ 2-7-98
Concurrence, Chair

drafted: dm/1.20.98/n20843tc.116

cc:
NDA Arch:
HFD-580/LRarick/Deputy Director/AMitra/MRhee
HFD-580/JMercier

Concurrence:
LPauls 01.23.98/AMitra 02.03.98