CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-843

CORRESPONDENCE

Moore
MAR 20 1997
MAR 20 1997

NDA 20-843

Schering Corporation
Attention: Joseph F. Lamendola, Ph.D.
Vice President,
U.S. Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07003

Dear Dr. Lamendola:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Prometrium (Progesterone, USP) Capsules
Therapeutic Classification:	Standard
Date of Application:	March 10, 1997
Date of Receipt:	March 11, 1997
Our Reference Number:	20-843

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 10, 1997, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Diane Moore, Consumer Safety Officer, at (301) 827-4260.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely.

/S/

3/19/97

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

cc:
Original NDA 20-843
HFD-580/Div. Files
HFD-580/CSO/D.Moore
HFD-580/LRarick/HJolson/CCropp/Tvander Vlugtt/MRhee/PStewart/KRaheja/AJordan
DISTRICT OFFICE

Drafted by: dm/March 17, 1997/n20843.fl

3/19/97

Concurrence:
LPauls 03.17.97

ACKNOWLEDGEMENT (AC)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-843

JAN 30 1998

Schering Corporation
Attention: Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, N.J. 07033

Dear Dr. Lamendola:

Please refer to your pending March 10, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prometrium (progesterone, USP) Capsules.

We have reviewed the submitted physician package insert and patient package insert for your submission dated March 10, 1997, and have several comments. Revisions have been incorporated directly into the enclosed package insert. Additions have been noted in redline, deletions have been noted as ~~strikeouts~~. Additional comments requiring response are in **14 pt bold face type**.

Please submit your revised package insert as soon as available so that we may continue the evaluation of your NDA.

If you have any questions, please contact Diane Moore, Project Manager at (301) 827-4260.

Sincerely,

/S/

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-843

MAR 11 1998

Schering Corporation
Attention: Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, N.J. 07033

Dear Dr. Lamendola:

Please refer to your new drug application dated March 10, 1997, received March 11, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prometrium (Progesterone, (USP) Capsules.

We also refer to your submissions dated March 14, July 17, 1997; and January 19, 1998.

The User Fee goal date for this application is March 11, 1998.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to:

> Submit data from the drug-drug interaction study as agreed upon in the meeting between the Division and representatives of your firm on November 1, 1996.

In addition, it will be necessary for you to submit revised draft labeling identical in content to the draft labeling submitted on March 10, 1997, with the revisions indicated in the Division's letter dated January 30, 1998. Please submit all revised labeling including the Physician's Insert, carton and containers.

Please note, further revisions to the labeling may be required based on the results of the drug-drug interaction study.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs. now will certainly facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Diane Moore, Project Manager, at (301) 827-4260.

Sincerely,

/S/

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

Moore

NDA 20-843

FEB 9 1998

Schering Corporation
Attention: Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, N.J. 07033

Dear Dr. Lamendola:

Please refer to your pending March 10, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prometrium (progesterone, USP) Capsules.

We also refer to our letter dated January 30, 1998, in which we incorporated revisions to your physician package insert and patient package insert.

Please find enclosed a diskette containing the revised revisions from the January 30, 1998, letter as you requested.

If you have any questions, please contact Diane Moore, Project Manager at (301) 827-4260.

Sincerely,

/S/ 2-4-98

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:
Diskette with labeling comments
from letter dated January 30, 1998

cc:
Original NDA 20-843
HFD-580/Div. Files
HFD-580/CSO/D.Moore
HFD-580/LRarick/Tvan der Vlugt/AMitra/MRhee/KRaheja/AJordan/KMeaker/LKammerman
HFD-580/Shaidar/ADorantes

Drafted by: dm/February 2, 1998/n20843ir.002

Concurrence:
LPauls, LRarick 02.03.98

INFORMATION REQUEST (IR)

/S/ 2/4/98

ORIGINAL

SCHERING CORPORATION

ORIG AMENDMENT

GALLOPING HILL ROAD KENILWORTH, N. J. 07033

CABLES: SCHERING KENILWORTH
TELEX: 138316
138280
TELEPHONE: (908) 298-4000

December 10, 1998

Lisa Rarick, M.D., Director
Division of Reproductive & Urologic Drug Products
Center for Drug Evaluation and Research
5600 Fishers Lane
HFD-580, Room 17B-45
Rockville, MD 20857

NDA20843
PROMETRIUM® Capsules
(progesterone, USP)

SUBJECT: LABELING REVISIONS REQUESTED BY FDA FOR PROMETRIUM® CAPSULES

Dear Dr. Rarick:

Schering Corporation is submitting revisions in response to changes requested to the PROMETRIUM® Capsules labeling during the October 28, 1998 teleconference and several phone conversations. Diane Moore also sent to Schering two faxes detailing the wording for "Pregnancy Category B" and "Carcinogenesis, Mutagensis, Impairment of Fertility" sections. All changes contained in this submission were discussed and agreed upon prior to this submission. This labeling was previously submitted for approval on August 28, 1998 and a "mocked-up" draft for further comment was submitted November 11, 1998.

Enclosed is a "mocked-up" copy (**Attachment 1**) with deletions noted as lined through text and additions noted as underlined text. A "clean" copy (**Attachment 2**) of the labeling is also enclosed which incorporates all the changes.

In addition, a desk copy of this submission and a computer disk copy (with the labeling file saved in Microsoft Word Version 7.0) have been forwarded to Ms. Diane Moore as per her request.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Rachael A. Stein

for Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

RS/hc

SCHERING CORPORATION DUPLICATE

GALLOPING HILL ROAD KENILWORTH, N. J. 07033

CABLES: SCHERING KENILWORTH
TELEX: 138316
138280
TELEPHONE: (908) 298-4000

ORIG AMENDMENT
AZ

August 26, 1998

Lisa Rarick, M.D., Director
Division of Reproductive & Urologic Drug Products
for Drug Evaluation and Research
5600 Fishers Lane
HFD-580, Room 17B-45
Rockville, MD 20857

NDA 20-843
PROMETRIUM® Capsules
100 mg (Progesterone)

SUBJECT: RESPONSE TO MARCH 11, 1998 APPROVABLE LETTER

Dear Dr. Rarick,

In response to your March 11, 1998 approvable letter, we are providing revised draft labeling for PROMETRIUM (progesterone, USP) Capsules, results of the drug-drug interaction study, and a new safety update. Details are provided below:

Revised Draft Labeling

Revisions to the labeling address all comments received in the January 30, 1998 FDA letter. The labeling has also been updated to include information from the labeling for PROMETRIUM Capsules approved under NDA 19-781, for the treatment of secondary amenorrhea.

We are providing a clean version (no markups) of the physician and patient package inserts in **Attachment 1.** The marked-up version of the labeling, which indicates any changes from the January 30, 1998 version, is provided in **Attachment 2.** Any deletions are noted by strike-through with a revision bar in the left or right margin, and any additions are noted with an underline and revision bar in the left or right margin. We are also providing an electronic copy of the clean version, in WORD 6.0. Final color flats of the bottle label, sample carton, and blister backing are provided in **Attachment 3.** This labeling is identical to the labeling approved under NDA 19-781 (PROMETRIUM Capsules for the treatment of secondary amenorrhea).

Under Dosage and Administration, the product is labeled for dosing in the evening. Our justification for evening dosing is for consistency with dosing in the pivotal clinical trial for this NDA, and for consistency with dosing for secondary amenorrhea (approved under NDA 19-781). In the pivotal trial for this NDA (PEPI Study H89-117), patients were instructed to take study medication in the evening. The dosing instructions are not included in the study protocol, but members of the PEPI coordinating center have informed us that the PEPI investigators were told to instruct study participants to dose their medication in the evening.

We have added an additional statement in the PRECAUTIONS, General section to alert physicians to an incidence of extreme dizziness and/or drowziness during initial use of this product. For these women, we recommend bedtime dosing. This addition is based on post-marketing reports we have recently received in the US. This data is consistent with the information submitted in our first quartery report to NDA 19-781.

We wish to discuss deletion of the Pregnancy Category X in the Pregnancy subsection under PRECAUTIONS. This is for consistency with other recently approved progesterone products.

Safety Update

Review of new safety information does not reveal any new safety concerns, nor change any safety conclusions from data provided in the NDA. There is no new clinical study information to report. An updated literature search and an updated summary of post-marketing experience are provided.

Study Report for Drug-Drug Interaction Study C97-342

We are providing the final study report for Study C97-342 entitled "SCH 961: A Study Evaluating The Interaction Between Progesterone (PROMETRIUM®) And Premarin®."

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Paula E Reynolds

for/ Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

PR/mv
Desk Copy: Diane Moore (Cover letter and Diskette)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Schering Corporation	August 26, 1998
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(908) 740-2628	(908) 740-2243

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*

2000 Galloping Hill Road
Kenilworth, New Jersey 07033

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

Joseph F. Lamendola, Ph.D.
Vice President
2000 Galloping Hill Road
Kenilworth, NJ 07033

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 20-843

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
progesterone, USP	PROMETRIUM®

CHEMICAL/BIOCHEMICAL /BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Pregna-4-ene-3, 20 dione	SCH 961

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Soft Gelatin Capsule	100 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Prevention of endometrial hyperplasia in non-hysterectomized post-menopausal women who are receiving conjugated estrogen tablets.

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING, AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION
Response to March 11, 1998 Approvable Letter - Revised Draft Labeling

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED_____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current pplication)

SCHERING CORPORATION

GALLOPING HILL ROAD KENILWORTH, N.J. 07033

CABLES: SCHERING KENILWORTH
TELEX: 138316
138280
TELEPHONE: (908) 298-4000

ORIGINAL

ORIG AMENDMENT

BC

January 19, 1998

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research
5600 Fishers Lane, HFD-580, Room 17B-45
Rockville, MD 20857

NDA 20-843
PROMETRIUM®
(progesterone, USP) Capsules

SUBJECT: RESPONSE TO FDA REQUEST

Dear Dr. Rarick:

This is in response to a request for information, received by telephone from Ms. Diane Moore, CSO.

- Ms. Moore and Dr. Mitra requested that we submit a request for an Environmental Assessment categorical exclusion.

  The Environmental Assessment provided in the original application (submitted March 10, 1997) was prepared in accordance with the November 1995 "Guidance For Industry" on "The Submission of an Environmental Assessment in Human Drug Applications and Supplements." Since that time, guidance governing the format and content of Environmental Assessments has changed in accordance with the Federal Register Notice of July 29, 1997. As recommended by FDA in their phone call of January 16, 1998 we are hereby requesting a categorical exclusion pursuant to 21 CFR 25.31(b). This action is subject to categorical exclusion since the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. Please refer to the original application (NDA 20-843), Volume 1.2, Section 4A.3 (Environmental Analysis; Appendix 2) for the calculation of the Expected Introduction Concentration (EIC).

- Ms. Moore, Dr. VanderVlught, and Dr. Meaker requested that we provide the definition of the local reader, central reader, and arbiter as concerns the endometrial biopsy final diagnosis.

  Further to our telephone conference on November 17, 1997, the following procedure was used to read the endometrial biopsies for PEPI Study H89-117:

  After evaluating the slide themselves, the local reader sent the slide to the central reader. The central reader telephoned the local site with the result. If a discrepancy existed, the local reader instructed the central reader to forward the slide to the umpire (arbiter) for evaluation. The umpire informed the local site of the reading. If the reading was again in disagreement with the other two readings, the local physician made a determination (with no official guidelines to follow) of the final diagnosis.

  Regarding Center 1, Patient [redacted] when the umpire's reading was also different from both the local and central readers, a fourth evaluation (at the local site by a different pathologist) was made of the same slide, which resulted in a diagnosis of "proliferative endometrium". The local physician then recorded the final determination to be "normal" based on this finding. There is a note stating this result on file with the case.

In accordance with 21 CFR 314.60 (c), Schering Corporation certifies that a copy of this amendment is being sent to FDA's New Jersey District Office.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Paula C Rinaldi

for/ Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

PR/ml

Okahumpka, Florida 34762
USEPA ID No. FLD984258731
Air Permit No. AO-35-193817
Issuing Authority: Florida Department of Environmental Protection
Expiration Date: 10/31/96 (Title V Permit Application has been submitted and expiration date is extended by rule)

6.e. Expected Introduction Concentration

The calculation of the expected introduction concentration (EIC) is based on a fifth-year production estimate for Prometrium Capsules. It is estimated that approximately kilograms of progesterone will be manufactured in that year.

Metabolism was considered in the EIC calculation since progesterone is almost completely metabolized and excreted from the body. Approximately % of administered progesterone is generally recovered in the urine as conjugated pregnanediol. Included in this appendix is background information on the metabolism of progesterone and an analysis of the effect that the use of Prometrium Capsules will have on the progesterone levels in the environment based on excretion estimates in the United States.

Therefore, EIC (aquatic) = AxBxCxD

where:
A = production rate adjusted for metabolism in users (kg/yr)
B = reciprocal of flow to POTW's (1/L/day)*
C = conversion of years to days
D = conversion for kilograms to milligrams

EIC = (0.14x8,700 kg/yr)x(1/1.115x10^{11} L/day)x(1 yr/365 days)x(10^{6} mg/kg)

EIC = 2.8x10^{-5}mg/L = 2.8x10^{-5} parts per million = 2.8x10^{-2} parts per billion

* 1.115x10^{11} liters per day entering publically owned treatment works (POTW). Source: 1992 Needs Survey, Report to Congress, Septmber 1993, EPA 832-R-93-002.

ORIGINAL

RV

SCHERING CORPORATION

CALLOPING HILL ROAD KENILWORTH, N. J. 07033

CABLES: SCHERING KENILWORTH
TELEX: 138316
138280
TELEPHONE: (908) 298-4000

ORIG AMENDMENT

December 15, 1998

Lisa Rarick, M.D., Director
Division of Reproductive & Urologic Drug Products
Center for Drug Evaluation and Research
5600 Fishers Lane
HFD-580, Room 17B-45
Rockville, MD 20857

NDA20843
PROMETRIUM® Capsules
(progesterone, USP)

SUBJECT: LABELING REVISIONS REQUESTED BY FDA FOR PROMETRIUM® CAPSULES

Dear Dr. Rarick:

Schering Corporation is submitting revised labeling incorporating a corrected figure as requested on December 11, 1998 during a FDA and Schering teleconference. In addition, Diane Moore requested a wording change on December 14, 1998 to the "Description" section. Ms. Moore recommended the following wording for the first sentence following the chemical structure: "Progesterone is synthesized from a starting material from a plant source and is chemically identical to progesterone of human ovarian origin."

Enclosed is a "mocked-up" copy (**Attachment 1**) with deletions noted as lined through text and additions noted as underlined text. A "clean" copy (**Attachment 2**) of the labeling is also enclosed which incorporates all the changes.

In addition, a desk copy of this submission and a computer disk copy (with the labeling file saved in Microsoft Word Version 7.0) have been forwarded to Ms. Diane Moore as per her request.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Rachael A. Ste

for Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

RS/hc

BL

ORIGINAL

SCHERING CORPORATION

ORIG AMENDMENT

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033
TELEPHONE: (908) 298-4000

November 11, 1998

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research
5600 Fishers Lane, HFD580, Room 17B-
Rockville, MD 20857
Attn: Document Control Room
FDA, CDER, ODE5

NDA 20-843
PROMETRIUM Capsules
(Progesterone, USP)

SUBJECT: RESPONSE TO REQUEST FOR LA[illegible]NGES

Dear Dr. Rarick:

Please find enclosed draft "mocked-up" labeling for PROMETRIUM Capsules, 100 mg, for the HRT indication. These changes are being made as per our teleconference with FDA held on October 28, 1998. On this "mocked-up" version, deletions are noted by strikeout and additions are noted by underlining.

The major revision to this labeling from the draft submitted on August 24, 1998, is the change from Pregnancy Category X to Pregnancy Category B. The wording for this section is on page 19 and is being submitted here for the first time.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Sincerely,

Rachael A. Stitt

Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

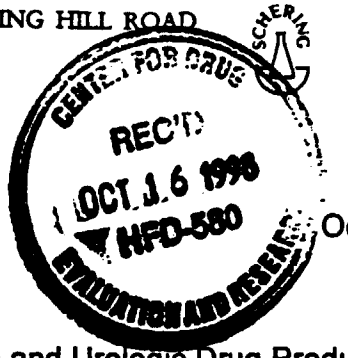
cc: Desk Copy- Diane Moore

ORIGINAL (BC) ORIG AMENDMENT

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000



October 14, 1998

Please The referral for source for progesterone is confirmed.

Ms. Diane Moore
Division of Reproductive and Urologic Drug Products
for Drug Evaluation and Research
5600 Fishers Lane
HFD-580
Rockville, MD 20857

NDA 20-843
PROMETRIUM®
(Progesterone, USP)
Capsules

10-21-98

Noted kr 10/22/98

SUBJECT: SYNTHESIS OF PROMETRIUM®

Dear Ms. Moore:

Schering Corporation is submitting information regarding the synthesis of Prometrium® as per your request on October 2, 1998. Please find attached a letter referencing the US Drug Master File which provides detailed manufacturing information.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Rachael A. Stein

for Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

RS:mv
Attachment

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

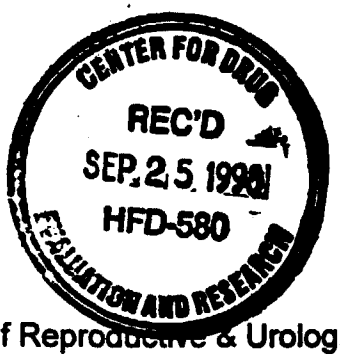
J:\OPS\SUBMIT\USRA\NDA\20843\LETTERS\101498.DOC

SCHERING CORPORATION

ORIGINAL

GALLOPING HILL ROAD KENILWORTH, N. J. 07033

CABLES: SCHERING KENILWORTH
TELEX: 138316
138280
TELEPHONE: (908) 298-4000



September 24, 1998

Division of Reproductive & Urologic Drug Products
for Drug Evaluation and Research
5600 Fishers Lane
HFD-580, Room 17B-45
Rockville, MD 20857
Attn: Ms. Diane Moore

NDA 20-843
PROMETRIUM® Capsules
100 mg (Progesterone)

SUBJECT: RESPONSE TO REQUEST

Dear Ms. Moore:

Per your request enclosed please find the disk with a clean version of the physician and patient package inserts. We have enclosed an additional disk in case you have any problems with it.

Sincerely,

Tonya L. Johnson

Tonya L. Johnson, Manager
U.S. Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

SCHERING CORPORATION

ORIGINAL

ORIG AMENDMENT

Noted for 2/9/98

GALLOPING HILL ROAD KENILWORTH, N. J. 07033

CABLES: SCHERING KENILWORTH
TELEX: 138316
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SU

July 17, 1997

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
HFD-580, Room 17B-45
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

NDA 20-843
PROMETRIUM®
(progesterone, USP) Capsules

Reviewed and Recorded
J. H. van der Vlugt
1/19/98

SUBJECT: FOUR-MONTH SAFETY UPDATE REPORT

Dear Dr. Rarick:

We are submitting the Safety Update Report for PROMETRIUM (progesterone, USP) Capsules, four months after the original NDA submission date of March 10, 1997.

This safety update contains information on three Phase IV post-marketing clinical studies conducted in Canada, and an update of post-marketing adverse experiences from Besins-Iscovesco and Schering-Plough. The data is provided separately rather than being combined in an overall analysis with the NDA data, since the three studies presented are studies, of different design and duration than the studies previously submitted to the NDA.

The safety results of the studies included in this Safety Update Report are similar to the results of studies included in the original NDA, and do not alter the data and conclusions in the original integrated summary of safety information. These data show a low incidence of adverse events and did not show any unexpected experience or increase frequency of commonly observed events in patients treated with progesterone. Therefore, there is no new information that would affect the statement of contraindications, warnings, precautions, and adverse reactions as submitted in the draft labeling in the original NDA.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Paula E Rinaldo

for/ Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

PER:dm

SCHERING CORPORATION

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...LOPING HILL ROAD KENILWORTH, N.J. 07033

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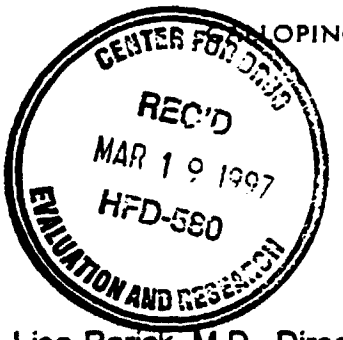

AJ 4/4/97

March 14, 1997

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
HFD-580, Room 17B-45
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

NDA 20-843
PROMETRIUM®
(progesterone, USP) Capsules

SUBJECT: ELECTRONIC FILES FOR ORIGINAL NEW DRUG APPLICATION

Dear Dr. Rarick:

As indicated in our March 10, 1997 cover letter to the subject Original New Drug Application, we are providing three diskettes containing electronic WordPerfect files for clinical pharmacology and clinical sections as requested during our August 28, 1996 meeting.

The first diskette contains the following clinical pharmacology information:

- Study report for C90-557 - (A Three-Cycle, Double-Blind, Dose Response Efficacy and Safety Study of the Endometrial Histologic Effects of Oral Micronized Progesterone (SCH 961) Compared to Placebo in Estrogen Primed Postmenopausal Women)
- Study report for Study 3 - Simon (Pharmacokinetics of Utrogestan 200 mg Administered Orally Once Daily for Two Days Compared to Progesterone in Oil 50 mg Administered Intramuscularly Once Daily for Two Days)
- Study summaries as provided in Section 6.B. on pages 1 to 15 of the NDA
- NDA Section 6.A., Human Pharmacokinetics and Bioavailability Summary

The second diskette contains:

- NDA Section 8.H., Integrated Summary of Safety
- NDA Sections 2 and 3.A., Labeling (included annotated versio...

Noted
J.Z. Vander Velde
4/2/97

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

The third diskette contains:

- Study report H89-117 - Postmenopausal Estrogen/Progestin Intervention (PEPI) Study

The diskettes are provided only in the desk copy to Ms. Diane Moore.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Paula E Lamendola

for/Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

PER:dm

Desk Copy: Ms. Diane Moore (HFD-580, Room 17B-45) - cover letter and diskettes.