WYETH-AYERST RESEARCH

P.O. BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

ORIGINAL

November 10, 2000

NDA No. 20-527/S-017
Prempro ™ (conjugated estrogens/medroxyprogesterone acetate tablets)
Premphase ® (conjugated estrogens/medroxyprogesterone acetate tablets)
Information Amendment
(Tradename proposal)

Susan Allen, M.D., Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Building, Room 17B-45
5600 Fishers Lane
Rockville, MD 20857

SUPPL NEW CORRESP

SNC-017

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
NOV 13 2000
HFD-580

Dear Dr. Allen:

Reference is made to NDA No. 20,527/S-017 for Prempro (conjugated estrogens(CE)/medroxyprogesterone acetate tablets(MPA)), Premphase (conjugated estrogens/medroxyprogesterone acetate tablets). In the Supplemental NDA No. 20-527/S-017 submitted to FDA on June 15, 2000, it was stated that a new tradename for the Low Dose products would be proposed as an amendment to the SNDA.

This submission amends S-017 and provides Wyeth-Ayerst's proposal and rationale for the tradename [redacted] for Low Dose CE/MPA (0.45mg/1.5mg and 0.3mg/1.5mg).

[redacted] ™ is proposed as the tradename for the new Low Dose CE/MPA products to help physicians accurately prescribe the appropriate dosage of CE/MPA for their patients since these new products consist of different estrogen and progestin dosages than the marketed PREMPRO products.

The initial NDA for PREMPRO/PREMPHASE single combined tablets (NDA No. 20-527) was approved in November 1995. Because 0.625 mg/2.5 mg was the only dosage approved for PREMPRO initially, physicians became accustomed to prescribing PREMPRO without a dosage designation. With the approval of PREMPRO 0.625 mg/5 mg in January 1998, it became necessary for physicians to designate the dosage for MPA (2.5 or 5 mg) when prescribing PREMPRO. Experience with PREMPRO has revealed that despite our efforts in educating physicians on the need to designate the dosage, confusion exists among physicians when designating the dosage of PREMPRO i.e, the MPA dosage is not always designated. This has resulted in dosage clarifications with physicians by pharmacists.

We believe that it is important from a prescribing perspective to differentiate the Low Dose CE/MPA products from PREMPRO 2.5 and 5. The introduction of Low Dose CE/MPA 0.45/1.5 and 0.3/1.5 using the tradename PREMPRO would cause even further confusion in prescribing the desired dosage. Contrary to PREMPRO 2.5 and PREMPRO 5, which differ in MPA dosage, the proposed dosages for Low Dose CE/MPA differ in the dose of CE only (MPA dose remains the same). If the new Low Dose CE/MPA products are launched under the existing PREMPRO tradename, it would require physicians to designate the CE dosage and the MPA dosage when prescribing the desired dose, i.e., 4 products consisting of 3 different strengths of CE in combination with 3 different strengths of MPA would be available as PREMPRO. It would be very difficult to educate physicians to change their prescribing habits in an environment where prescribing practice has already been established for PREMPRO, i.e., PREMPRO 2.5 or PREMPRO 5. Keeping in line with FDA's announcement of plans to publish a draft guidance on Evaluating Proprietary Names in order to avoid medication errors, published in *The Pink Sheet*, March 27, 2000, the tradename [redacted] is being proposed for the new Low Dose CE/MPA products to differentiate the Low Dose products from PREMPRO and thus avoid further dosage confusion. For the Low Dose CE/MPA products, physicians may designate the dose by prescribing the dose of CE, i.e., [redacted]

In evaluating this proposal it is requested that the committee take into consideration that separate tradenames for products with the same active ingredients, but different dosages, have previously been approved. This list includes: oral contraceptive products such as Nordette and Alesse, Ortho-Novum 1/35 and Modicon, Norinyl and Brevicon and the rheumatoid and osteoarthritic drugs, Orudis and Oruvail.

If you have any questions regarding this submission, please contact the undersigned at (610) 902-3749 or Dr. Joseph Sonk at (610) 902-3740.

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman, Manager
Women's Healthcare
Worldwide Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

WYETH-AYERST RESEARCH

PO BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

October 31, 2000

NDA 20-527/S-017 ORIGINAL

Susan Allen, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Attention: Document Control Room 17B-20 SUPPL NEW CORRESP
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SNIC-017

Dear Dr. Allen:

Please refer to our approved NDA 20-527 for Prempro/Premphase and in particular S-017. This letter serves as notification that effective immediately, Ms. Jennifer D. Norman is the correspondent for NDA 20-527/S-017. Ms. Norman can be contacted at:

Ms. Jennifer Norman, Manager
Women's Healthcare
Worldwide Regulatory Affairs
Wyeth-Ayerst Research
P.O. Box 8299
Philadelphia, PA 19101-8299
Phone: (610) 902-3749
Fax: (610) 964-5969

If there are any questions, please contact the undersigned at (610) 902-3740.

Sincerely,

Joseph S. Sonk, Ph.D., Senior Director
Global Therapeutic Area Head
Women's Healthcare
Worldwide Regulatory Affairs

JJS:lad\0005

Desk Copy: Ms. Diane Moore

WYETH-AYERST RESEARCH

P.O. BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

ORIGINAL

October 24, 2000

[redacted]

Premarin (conjugated estrogens tablets, USP)

NDA No. 20-527/S-017
Prempro (conjugated estrogens/medroxyprogesterone acetate tablets)
Premphase (conjugated estrogens/medroxyprogesterone acetate tablets)

General Correspondence

Susan Allen, M.D., Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Building, Room 17B-45
5600 Fishers Lane
Rockville, MD 20857

NDA SUPP AMEND

S(-2-115-13B

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 25 2000
HFD-580

Dear Dr. Allen:

Reference is made to NDA No. 04-782/S-115 for Premarin (conjugated estrogens tablets, USP) and NDA No. 20-527/S-017 for Prempro (conjugated estrogens/medroxyprogesterone acetate tablets), Premphase (conjugated estrogens/medroxyprogesterone acetate tablets).

In response to Ms. Diane Moore's request by telephone on October 17, 2000 for additional pharmacokinetic information as electronic files pertaining to NDA No. 04-782/S-115, enclosed with this submission are the following:

- Pharmacokinetics data for study 0713D2-119-US (hard copy previously submitted in support of these supplements) electronically in ASCII format with user guide (2 CDs are enclosed).
- Individual study report (GMR 32506) for 0713D2-119-US electronically in Word 97 on the same CDs as above.
- The Human Pharmacokinetics and Bioavailability Summary – Item 6.1 of NDA 04-782/S-115 – electronically in Word 97 (2 disks are enclosed).
- Dissolution data on the clinical lot and registration lots submitted in NDA 04-782/S-017 for Premarin Tablets 0.45 mg using USP 24 and the proposed modified USP 24 method with sinker weights will be provided by January 12, 2001 as requested by Ms. Moore.

In addition to the above, pk data for study 0713D2-120-US (hard copy previously submitted in support of NDA No. 20-527/S-017) electronically in ASCII format with user guide and individual study report (GMR 32507) electronically in Word 97 are also provide on the same disks/CDs in response to a previous request.

WYETH-AYERST RESEARCH

P.O. BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

ORIGINAL

301

October 16, 2000

NDA No. 20-527/S-017
Conjugated Estrogens/Medroxyprogesterone Acetate Combination Tablets
4 Month Safety Update

Susan Allen, M.D., Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Building, Room 17B-45
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

CENTER FOR DRUG
REC'D
OCT 17 2000
HFD-580
EVALUATION AND RESEARCH

Dear Dr. Allen:

Reference is made to our NDA No. 20-527/S-017 previously submitted to your administration on June 15, 2000. This sNDA supports the use of two new lower doses of conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) in a continuous combined regimen for the treatment of moderate to severe vasomotor symptoms associated with menopause, and t — vulvar and vaginal atrophy.

The purpose of this submission is to provide the 4-Month Safety Update for the above referenced new drug application. This submission contains Item 9, 4-Month Safety Update with supportive tables and appendices. There are four appendices included in this submission. Appendix 1 appears in Volume 1; Appendices 2,3, and 4 appear in Volume 2. For a summary of this 4-Month Safety Update, please refer to the first page of the enclosed update.

All the Items in this submission are provided as hard copy.

Please note that all files were scanned for viruses using McAfee Virus Scan 4.0.3a software and no viruses were detected.

If you have any questions regarding this submission, please contact me at (610) 902-3749.

Sincerely,

WYETH-AYERST RESEARCH

Jennifer D. Norman

Jennifer D. Norman, Manager
Worldwide Regulatory Affairs

Desk Copy:
Mrs. Diane Moore, Project Manager

LTH-1013

NDA 20-527/S-017
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg and 0.45 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

October 10, 2000 submission

The October 10, 2000, submission cover page is currently missing.

WYETH-AYERST RESEARCH

PO BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

U S REGULATORY AFFAIRS

ORIGINAL

August 14, 2000

NDA No. 20-527 S-017
Conjugated Estrogens and Medroxyprogesterone Acetate Combination Tablets

General Correspondence

Susan Allen, MD, Acting Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Attention: Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Allen.

Reference is made to NDA No. 20-527 S-017 for Conjugated Estrogens and Medroxyprogesterone Acetate Combination Tablets.

Additional reference is made to the April 20, 2000 teleconference with the Division to discuss Wyeth-Ayerst proposals regarding the electronic presentation of Item 11 (NDA No. 20-527 S-017).

Attached are the minutes of this meeting as prepared by Wyeth-Ayerst.

If you have questions regarding this submission, please contact the undersigned at (610) 902-3731 or Dr. Joseph Sonk at (610) 902-3740.

Sincerely,

WYETH-AYERST LABORATORIES

JoAnne M. Bissinger
Manager, Worldwide Regulatory Affairs

4-20-00 FDA Item11 letter.doc

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
Wyeth-Ayerst Laboratories	August 14, 2000
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(610) 902-3731	(610) 964-5973
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code telephone & FAX number)* IF APPLICABLE
P.O. Box 8299 Philadelphia, PA 19101	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-527

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Conjugated estrogens/medroxyprogesterone acetate (CE/MPA)	To Be Determined

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	0.3 mg CE/1.5 mg MPA & 0.3 mg CE/1.5 mg MPA	Oral

(PROPOSED) INDICATION(S) FOR USE:

Treatment of vasomotor symptoms associated with menopause. Treatment of vulvar and vaginal atrophy

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 31.94)
☐ 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 Provides Wyeth- Minutes of a 4-20-00 Teleconference with the Division

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

NUMBER OF VOLUMES SUBMITTED - 1

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 application)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50(c))
	4. Chemistry section
	A. Chemistry, manufacturing; and controls information (e.g. 21 CFR 314.50(d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (I), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2) Electronic copy only
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2) Electronic copy only
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355 (b) (2) or (j) (2) (A)
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.50(k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify) A) Financial Disclosure B) Pediatric Rule (Waiver Request)

CERTIFICATION

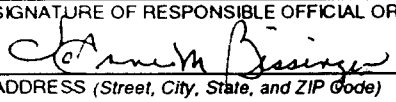
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	JoAnne M. Bissinger, Manager, Worldwide Regulatory Affairs	August 14, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
P.O. Box 8299 Philadelphia, PA 19101	(610) 902-3731

Please **DO NOT RETURN** this form to this address.

MEMORANDUM OF TELECONFERENCE

sNDA No. 20-527

Conjugated Estrogens (CE)/Medroxyprogesterone Acetate (MPA)

April 20, 2000

ATTENDEES:

FDA

Lisa Kamerman, PhD	Team Leader, Division of Biometrics II at DRUDP
Diane Moore	Project Manager, Division on Reproductive and Urologic Drug Products (DRUDP)

Wyeth-Ayerst

Paul Hansen	IT Engineer, Global Clinical Programming
Michelle Lucas	Senior Statistician, Global Clinical Biostatistics
Mary Beth Thompson	Standards Manager, Global Regulatory Information & Documentation
Joseph S. Sonk, PhD	Senior Director, Therapeutic Area Head Women's Health, Worldwide Regulatory Affairs
JoAnne M. Bissinger	Manager, Worldwide Regulatory Affairs

Background

Wyeth-Ayerst is preparing an efficacy supplement to NDA 20-527 [Conjugated Estrogens (CE)/ Medroxyprogesterone Acetate (MPA)] which will provide endometrial hyperplasia, metabolic and vasomotor data from an interim analysis of the HOPE Study (Protocol No. 713B-309-US, [redacted]

Since there are 3 separate patient populations in the HOPE study {A-Main population (2673 patients, 57 sites), B-Patients of a disqualified investigator (48 dosed + 3 without study medication) and C-Other patients without study medication (81 patients from the investigators included in 11A)} a teleconference with the FDA was requested to discuss Wyeth-Ayerst's proposal to reduce the number of files in Item 11, Case Report Tabulations.

Our proposals were faxed to the Division on July 18, 2000 (Attachment I). In addition, the proposals were e-mailed to Mr. Randy Levin, (Associate Director Electronic Submissions, Office of the Center Director). His e-mail response (Attachment II) is incorporated in this document, although he did not attend the meeting.

Summary

The follow documents the proposals and FDA's responses.

Proposal 1

Rather than create 1 SAS XPORT file for each domain in each of the three populations (3 total files per domain), we will create 1 xport file per data domain which will include patients from all three populations with indicator variables on the dataset which will specify whether the patient is in 11A, 11B, or 11C. This strategy reduces the number of files by a factor of three.

Dr. Kamerman and Mr. Levin agreed to the following:

The three unique patient populations will be combined in the SAS XPORT files, and the patients in each population can be selected by the FDA using the following criteria:

A) Main population with reported study medication (n=2673).
Select patients where investigator number is not 30952 and duration of study is greater than or equal to 1 day.

B) Disqualified investigator, patients with reported study medication (n=48).
Select patients where investigator number is 30952 and duration of study is greater than or equal to 1 day.

C) Patients with no reported study medication (n=84).
Select patients where duration of study is not greater than or equal to 1 day (in SAS terms, a missing value for duration).

Proposal 2
Some of the domains will require more than one 25 MEG SAS XPORT file (e.g. lab data approximately six (6) 25 MEG files; with daily bleeding and vasomotor symptoms data approximately sixty (60) 25 MEG files). We propose to assign the data for unique groups of investigators to each file based on grouping the investigators by sequential investigator numbers which will result in approximately equal size files. Some investigators will have bleeding and symptoms data that will exceed 25 MEG and will be assigned to separate XPORT files based on groups of sequential patient number for that investigator.

Mr. Levin suggested that the laboratory values be put in smaller groups (e.g., electrolytes, LFTs, etc.) before dividing them by investigator with separate files for the bleeding and vasomotor symptoms data. Wyeth-Ayerst (W-A) believes that the large number of records in the study will not divide well into the suggested categories and that the W-A's proposal is the best choice.

Dr. Kamerman agreed to the following:

For any data domain (e.g. labs, daily bleeding and vasomotor symptoms, etc.) which will require more than one 25 MEG SAS XPORT file, the data will be subdivided into two or more XPORT files. Each of these files will include approximately 25 MEG of data based on unique groups of investigator numbers, and, if need be, based on unique groups of patient numbers within one investigator.

Sex, age, and ethnic origin will be the only demographic data to be included in the SAS XPORT files for all data domains. Additional patient data (e.g. baseline height, weight, body mass index, years since menopause, duration of study, etc.) will be included in the XPORT file for demography and patient characteristics so that the FDA can merge this data with the data from any XPORT file if need be for selecting patients based on any of these characteristics.

The data analysis files (e.g. derived bleeding/vasomotor symptom data used in statistical analyses by biostatistics) will also be provided in the form of SAS XPORT files which will incorporate the criteria above.

Attachment I

FACSIMILE TRANSMISSION
WYETH-AYERST RESEARCH
US Regulatory Affairs
170 Radnor Chester Road
St. Davids, PA 19087

Telefax Number: (610) 964-5973

DATE: *April 18, 2000*

TO: ***Diane Moore***
Division of Reproductive and Urologic Drug Products

FACSIMILE No: *1-301-827-~~4267~~ 4272*

FROM: *JoAnne M. Bissinger*
U.S. Regulatory Affairs
(610) 902- 3731

NO. of PAGES: *2 (including cover page)*

SUBJECT: *Efficacy Supplement for NDA 20-527*
(Conjugated Estrogens/ Medroxyprogesterone Acetate)

Diane,

As I indicated in our conversation today, Wyeth-Ayerts is preparing an efficacy supplement to NDA 20-527 regarding data from the HOPE Study [redacted] which will be submitted in second quarter 2000, and that we have a couple of question regarding the electronic submission of Item 11. The following is a summary of those questions.

HOPE Study Patient Populations:

11A *Main population (2673 patients, 57 investigators)*
11B *Patients of disqualified investigator (48 dosed + 3 without study medication, investigator 30952)*
11C *Other patients without study medication (81 patients from investigators included in 11A)*

Proposals

1) Rather than create 1 SAS XPORT file for each data domain in 11A, 11B, and 11c (3 total files per domain), we will create 1 XPORT file per data domain which will include patients from 11A, 11B, and 11C with an indicator variable on the dataset which will specify whether the patient is in 11A, 11B, or 11C. The purpose of this is to reduce the number of files by a factor of three.

2) Some of the domains will require more than one 25 MEG SAS XPORT file (e.g. lab data approx 6 25 MEG files, daily bleeding and vasomotor symptom data approx 60 25 MEG files). We propose to assign the data for unique groups of investigators to each file based on grouping the investigators by sequential investigator numbers (e.g. 30901 to 30910, 30911 to 30916, 30917 to 30918, etc.) which will result in appoximately equal sized files. Note that some investigators have so much bleeding and symptom data, that their data will excced 25 MEG and will have to be assigned to separate XPORT files based on groups of sequential patient numbers for that investigator (e.g. 30918 pts 0001 to 0050, 30918 pts 0051 to 0100, 30918 pts 0101 to 0145).

A meeting is scheduled for Thursday, April 20, 2000 at 9:30 am
The ATT dial in number is 1 (800) 486-2460 ***Participant Code: 129427***

If you have any questions, please don't hesitate to call me at (610) 902-3731.

JoAnne M. Bissinger

FDA R&Ufax.doc

APPEARS THIS WAY
ON ORIG

Attachment II

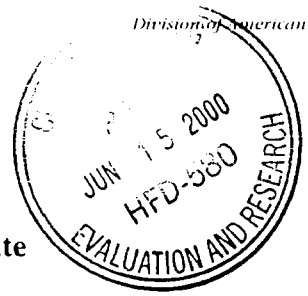
WYETH-AYERST RESEARCH

PO BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

ORIGINAL



June 15, 2000

NDA No. 20-527
Conjugated Estrogens and Medroxyprogesterone Acetate Combination Tablets

Labeling Supplement:
Lower Combination Doses

Susan Allen, MD, Acting Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Attention: Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

20-527 SE2 SLR-017
NDA NO. _____ REF. NO. _____
NDA SUPPL FOR Labeling

Dear Dr. Allen,

In accordance with 21 CFR §314.50 and §314.70(b), Wyeth-Ayerst Laboratories hereby submits a Supplemental New Drug Application for Conjugated Estrogens and Medroxyprogesterone Acetate Combination Tablets.

Marketing approval is being sought for two new lower doses of conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) [0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA] in a continuous combined regimen for the treatment of moderate to severe vasomotor symptoms associated with menopause, and ——— vulvar and vaginal atrophy.

This supplemental NDA provides safety and effectiveness data regarding postmenopausal symptoms, endometrial and metabolic parameters for lower doses of CE/MPA from the planned 1-year interim analysis of Protocol No. 713B-309-US[1] (the HOPE study), and is **not** meant to satisfy the December, 1994 Phase IV commitment relative to the minimum effective dose for the prevention of osteoporosis. The establishing of the minimum effective dose for the prevention of osteoporosis will be the subject of a separate Supplemental New Drug Application, submitted in a timely manner upon the completion of the HOPE study, currently anticipated to complete in 4Q 2000.

[1] Subsequently designated as 713**D2**-309-US. The project code, 713B, was changed to 713D2 in order to comply with a new protocol numbering system.

Clinical Study Background

Wyeth-Ayerst proposed to conduct a Phase IV clinical trial to define the minimum effective dose of the combination of conjugated estrogens and medroxyprogesterone acetate for the prevention of osteoporosis, during the October 5, 1993 meeting with the Division of Metabolism and Endocrine Drug Products (DMEDP) to discuss the filing of NDA No. 20-303 (Conjugated Estrogens and Medroxyprogesterone Acetate Separate Tablets). Several teleconferences and a face-to-face meeting were held with the Division to agree upon the final study design. The final protocol, 713B-309-US, was submitted on July 18, 1995.

This 8-arm, double blind (double-dummy), placebo and active-controlled, multicenter, out-patient trial is a 2-year study of lower-dose combinations of conjugated estrogens and medroxyprogesterone acetate in postmenopausal women. The primary objective of the first year of treatment (basic study) was to evaluate the safety and efficacy of lower doses of CE/MPA in reducing the incidence of endometrial hyperplasia associated with the use of unopposed estrogen. The secondary objective was to evaluate the efficacy of lower doses of CE/MPA in relieving menopausal vasomotor symptoms; the effects on vaginal maturation were also assessed.

The primary objective for the two-year treatment (Osteoporosis and Metabolic Substudy) is to evaluate the safety and effectiveness of lower dose combinations of CE/MPA in the prevention of postmenopausal bone loss; metabolic data will also be analyzed .

The products being studied in the 8 treatment arms are as follows:

CE oral tablets: 0.3 mg, 0.45 mg, and 0.625 mg
CE/MPA oral tablets: 0.3mg/1.5 mg, 0.45 mg/ 1.5, 0.45mg/2.5 mg, and 0.625 mg/2.5 mg
Placebo

Please recall that in a December 9, 1999 submission [redacted]
Wyeth-Ayerst provided a document entitled "Unblinding Procedures for Interim Analysis of the HOPE Study (713B-309-US)" which defined the unblinding strategy for the 1-year interim analysis. On December 16, 1999, Mrs. Diane Moore (Project Manager, DRUDP) telephoned JoAnne M. Bissinger (Wyeth-Ayerst) and indicated that the medical and statistical reviewers agreed that the unblinding procedures were appropriate. These procedures were implemented during the unblinding for the interim analysis.

Tradename/Physician & Patient Labeling

Since the initial approval for Prempro™ (November 11, 1995; Original NDA No. 20-527) was for only one dosage strength (0.625 CE/2.5 MPA continuous combination tablet), physicians typically prescribed Prempro without dosage identification. With the approval of a second Prempro dosage strength on January 9, 1998 (0.625 CE/5 mg MPA continuous combination tablet) it is our belief that confusion regarding the dosage to be dispensed by pharmacists has occurred, since some physicians may continue to prescribe Prempro without clearly indicating the MPA dose.

Thus, in an effort to minimize dosage confusion, Wyeth-Ayerst is proposing to use a new tradename for the lower doses of CE/MPA. (Proposed trademark(s) will be submitted, shortly, as an amendment to this SNDA for FDA review.) Accordingly, the draft Physician & Patient Labeling provided in this SNDA is specific to the lower doses of CE/MPA combination tablets provided for in this supplement and does not include the currently approved Prempro dosage strengths.

User Fee
User Fee ID No. 3947 has been preassigned to this application. A check for 100% of the required fee ($142,870.00) for supplements requiring clinical data has been submitted to the Mellon Bank, Pittsburgh, PA postal address designated for user fee payments.

Field Copy
In compliance with 21 CFR §314.50(1)(3), a field copy of the chemistry, manufacturing and controls (CMC) was sent to the Philadelphia District Office (Ms. Debra Pagano) on June 15, 2000.

Supplement Contents
In addition to the applicable Technical Sections, this supplement contains an abbreviated Application Summary consisting of draft annotated labeling, Chemistry, Manufacturing and Controls Summary, Human Pharmacokinetics and Bioavailability Summary, Clinical Data Summary and Results of Statistical analysis, and a Discussion of Benefit/Risk Relationship.

Item 11 Case Reports Tabulations
A teleconference was held with the Division on April 20, 2000 to discuss the electronic submission of Item 11 (Case Reports Tabulations). As agreed, one SAS XPORT file per data domain will include all patients in the study. Indicator variables on the files will identify patients included in each of the 3 populations (main study, patient of a disqualified investigator, and other patients who did not take study medication). The files are divided by investigator and sequential patient numbers. All demographic variables are included in the demographic data set; only demographics for gender, age, and ethnic group are included in other files. An analysis data set for relief of moderate to severe vasomotor symptoms is also included.

The supplement contents are as follows:

Item No.	Description	Volume No.
1	Index	1
2	Labeling	2
3	Application Summary	3
4	Chemistry, Manufacturing and Controls	4 - 18
6	Human Pharmacokinetics and Bioavailability	19 - 35
8	Clinical	36 - 70
I0	Statistical	71 - 88
11	Case Report Tabulations	electronic copy only
12	Case Report Forms	electronic copy only
13	Patent and Exclusivity Information	1
16	Debarment Certification	1
17	Field Copy Certification	1
18	User Fee Cover Sheet	1
19	Other: A) Financial Disclosure, B) Pediatric Rule (Waiver Request)	1

If you have questions regarding this submission, please contact our representative, Miss JoAnne M. Bissinger, at (610) 902-3731 or the undersigned at (610) 902-3740.

Sincerely,

WYETH-AYERST LABORATORIES

JoAnne M Bissinger
for

Joseph S. Sonk
Senior Director,
Therapeutic Head, Women's Healthcare
Worldwide Regulatory Affairs

WYETH-AYERST RESEARCH

PO BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

June 15, 2000

NDA No. 20-527
Conjugated Estrogens and Medoxyprogesterone Acetate Combination Tablets

Ms. Debra Pagano
Program Coordinator for Field Copy Submissions
Room 900
Department of Health and Human Services
Food and Drug Administration
2nd and Chestnut Streets
Philadelphia, PA 19106-2973

Dear Ms. Pagono,

Reference is made to our approved New Drug Application No. 20-527 for Conjugated Estrogens and Medroxyprogesterone Acetate Combination Tablets.

In compliance with 21 CFR §314.50(1)(3), we hereby submit to the Philadelphia District Office a field copy of the chemistry, manufacturing and controls (CMC) information submitted in the aforementioned supplemental NDA.

Wyeth-Ayerst hereby certifies that the enclosed submission is a true copy of the CMC section, application form and the cover letter sent to Division of Urologic and Reproductive Drug Products located at the Food and Drug Administration offices in Rockville, Maryland.

Should you have any questions regarding the enclosed materials, please contact our representative, JoAnne M. Bissinger, at (610) 902-3731 or the undersigned at (610) 902-3740.

Sincerely,

WYETH-AYERST LABORATORIES

JoAnne M. Bissinger for

Joseph S. Sonk
Senior Director,
Therapeutic Head, Women's Healthcare
Worldwide Regulatory Affairs

HOPE 2000 Field Copy Letter.doc

LTR-1019

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
Wyeth-Ayerst Laboratories	June 15, 2000
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(610) 902-3740	(610) 964-5973
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: P.O. Box 8299 Philadelphia, PA 19101	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-527

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Conjugated estrogens/medroxyprogesterone acetate (CE/MPA)	To Be Determined

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	0.3 mg CE/1.5 mg MPA & 0.3 mg CE/1.5 mg MPA	Oral

PROPOSED INDICATION(S) FOR USE:

vasomotor symptoms associated with menopause. vulvar and vaginal atrophy

PLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 31.94)
☐ 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 Addition of Lower Doses

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

NUMBER OF VOLUMES SUBMITTED 88 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 application)

This application contains the following items: *(Check all that apply)*	
X	1. Index
X	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
X	3. Summary (21 CFR 314.50(c))
	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50(d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
X	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
X	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
X	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
X	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2) Electronic copy only
X	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2) Electronic copy only
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355 (b) (2) or (j) (2) (A)
	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k) (1))
X	17. Field copy certification (21 CFR 314.50(k) (3))
X	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) A) Financial Disclosure B) Pediatric Rule (Waiver Request)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
[signature]	Joseph S. Sonk, PhD, Senior Director, Therapeutic Head Women's Health, Worldwide Regulatory Affairs	June 15, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
P.O. Box 8299 Philadelphia, PA 19101	(610) 902-3740

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

Memorandum of Teleconference

Date: February 6, 2003

Time: 10:00 AM

Application: NDAs 20-527/S-017 and 04-782/S-115

Participants:

From Wyeth:

Ginger Constantine, MD, Vice-President Women's Healthcare CR&D
Joseph Sonk, PhD, Assistant Vice-President Women's Healthcare, WWRA
Diane Harrison, MD, Director, Women's Healthcare, CR&D
Robert Northington, PhD, Director, Clinical Biostatistics, CR&D
Simon Golec, PhD, Director, Women's Healthcare, CMC, WWRA
Jennifer Norman, Associate Director, Women's Healthcare, WWRA
Colleen Murray, Senior Regulatory Coordinator, Women's Healthcare, WWRA

From DRUDP:

Theresa van der Vlugt, M.D., M.P.H. – Repro, Medical Officer, DRUDP (HFD-580
Kassandra Sherrod, R.Ph., Regulatory Project Manager
David Lin, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Sarah Pope, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Background
The supplemental application 20-527/017 was resubmitted on September 11, 2002, received on September 12, 2002. The supplement proposes the use of 0.45 mg conjugated estrogen and 1.5 mg medroxyprogesterone acetate combination tablets in a continuous combined regimen for the treatment of moderate to severe vasomotor symptoms associated with the menopause and the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. The User Fee goal date is March 12, 2003. An approvable action was taken by DRUDP on April 13, 2001.

The supplemental application 04-782/S115 was resubmitted on October 28, 2002, received October 30, 2002. The supplement proposes the use of Premarin 0.45 mg for the treatment of moderate to severe vasomotor symptoms associated with the menopause and the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. The User Fee goal date is April 30, 2003. An approvable action was taken by DRUDP on July 31, 2001.

Meeting Objective:
To review the recommended changes to the Prempro SLR-017 draft labeling and the Premarin SLR-115 draft labeling.

Discussion Points:

- See attached labeling; additions are indicated by double underline and deletions are indicated by ~~strike through~~.

Action items:

- Sponsor will revise Tables 1, 2, and 3 of the Prempro label and submit.
- Sponsor will send SAS dataset for the proposed cumulative amenorrhea figure for Prempro.
- Sponsor will revise Tables 1 and 2 of the Premarin label and submit.
- Discussion on reclassification.

Signature, minutes preparer

Signature, Chair

cc: Original
HFD-580/20-527 Div. Files
HFD-580/04-782 Div Files
HFD-580/Slaughter, van der Vlugt, Lin, Pope, Parekh

Drafted: by KS/3.04.03
Initialed by:van der Vlugt, Pope, 3.5.03
Final: Sherrod, 3.10.03
TELECONFERENCE MEETING MINUTES

Number of Pages Redacted 54

Draft Labeling
(not releasable,

Memorandum of Meeting Minutes

Date:	February 4, 2003
Time:	10:30 AM
Application:	NDAs 20-527/S-017 and 04-782/S-115
Place:	Parklawn; 17B-43
Type of Meeting:	5-month status/labeling meeting
Meeting Chair:	Shelley R. Slaughter, M.D., Ph.D.
Meeting Recorder:	Kassandra Sherrod, R.Ph.

FDA Attendees:
Shelley Slaughter, M.D., Clinical Team Leader, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., Medical Officer, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Kassandra Sherrod, Project Manager, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
David Lin, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II)@ DRUDP (HFD-580)
Sarah Pope, Ph.D., Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Background
The supplemental application 20-527/017 was resubmitted on September 11, 2002, received on September 12, 2002. The supplement proposes the use of 0.45 mg conjugated estrogen and 1.5 mg medroxyprogesterone acetate combination tablets in a continuous combined regimen for the treatment of moderate to severe vasomotor symptoms and [redacted] vulvar and vaginal atrophy associated with menopause. The User Fee goal date is March 12, 2003. An approvable action was taken by DRUDP on April 13, 2001.

The supplemental application 04-782/S115 was resubmitted on October 28, 2002, received October 30, 2002. The supplement proposes the use of Premarin 0.45 mg for the treatment of moderate to severe vasomotor symptoms and [redacted] vulvar and vaginal atrophy associated with menopause.The User Fee goal date is April 30, 2003. An approvable action was taken by DRUDP on July 31, 2001.

Meeting Objective:
To review labeling comments for supplements 115 and 017.

Discussion Points:

- See attached labeling; additions are indicated by double underline and deletions are indicated by ~~strike-through~~.

Action items:

- PM to schedule T-Con with sponsor to discuss revisions made in the attached label.

Signature. minutes preparer

Signature, Chair

cc: Original
HFD-580 20-527 Div. Files
HFD-580 04-782/Div Files
HFD-580 Slaughter, van der Vlugt, Lin, Pope

Drafted: by KS/2.20.03
Initialed by van der Vlugt, 2.21.03/Lin, 2.27.03/Slaughter, Pope, 3.3.03
Final: Sherrod/3.3.03
MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 11

Draft Labeling
(not releasable,

Minutes of Teleconference

Date: April 16, 2001 **Time:** 10:00 – 10:15 AM **Location:** Parklawn; Ms. Moore's Office

NDA: 20-527/S-017 **Drug Name:** (conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) tablets, 0.45 mg CE/1.5 mg MPA and 0.3 mg CEE/1.5mg MPA

Type of Meeting: Labeling

External Constituent: Wyeth-Ayerst Research

Meeting Chair: Ms. Diane Moore

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Diane Moore – Regulatory Project Manager Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Participants:
Joseph S. Sonk, Ph.D. – Assistant Vice President, Worldwide Regulatory Affairs, Global Therapeutic Area Head, Women's Healthcare, Wyeth-Ayerst Laboratories
Cynthia Davidson– Senior Regulatory Coordinator, Worldwide Regulatory Affairs, Wyeth-Ayerst Laboratories

Background: On April 13, 2001, the Division of Reproductive and Urologic Drug Products sent Wyeth-Ayerst a letter for NDA 20-527, Supplement 017, which included requests for labeling revisions pertaining to that supplemental application. On April 16, 2001, representatives from Wyeth-Ayerst called Ms. Diane Moore, Project Manager, with questions regarding the proposed labeling revisions.

Meeting Objective:
To convey questions to the Division regarding the labeling comments in the April 13, 2001, agency letter.

Discussion Items:
- the sponsor requested a teleconference with the Medical Officer, Medical Team Leader and Project Manager to discuss the labeling comments from the April 13, 2001, letter
- the sponsor was informed that a written request for a meeting including the type of meeting requested, specific questions, a list of requested attendees, a proposed date for the meeting and background package are needed for teleconference requests; the sponsor indicated that they would like the teleconference as soon as possible
- the sponsor was informed that the Medical Officer was not available to discuss the granting or rejecting of the meeting request, but that the Division may grant a meeting by responding to specific questions in a meeting request
- the sponsor asked if the portion of the **HOW SUPPLIED** section that reads, "

could be

revised to read '

- the sponsor conveyed the following questions:
  1. In the **Clinical Studies** subsection, under **Information Regarding Effects on Vasomotor Symptoms,** why was the graph entitled "A deleted?
  2. Under **Information Regarding Effects on Vulvar and Vaginal Atrophy** section, why was the table deleted?
  3. In Table 5, INCIDENCE OF ENDOMETRIAL HYPERPLASIA AFTER ONE YEAR OF TREATMENT, why was the e footnotes a and b deleted?
  4. In the Clinical Studies section on the Effects on the Endometrium, in Table 5
  5. The sponsor ' as it is already in the approved labeling. Why was it deleted?
  6. Under the **WARNINGS** section, second paragraph, why was the last line deleted that reads,
  7. A paragraph was eliminated from the previous approved version. It began, ' . ." Why was it eliminated?
  8. Under the **PRECAUTIONS** section, subsection, which reads, ' why was this subsection deleted?
  9. Under **Carcinogenesis, Mutagenesis, and Impairment of Fertility** section, the fourth paragraph, why was the last sentence that reads ' deleted?

Decisions reached:

- Ms. Moore informed the sponsor that the section in the **HOW SUPPLIED** section is being standardized by the chemists and the revisions to that section is the same as for other labels; the sponsor indicated that they would agree to those recommendations
- Ms. Moore noted that the referenced case of endometrial hyperplasia was determined to be cancer; that issue needs further clarification from the Medical Officer
- the sponsor agreed to provide the questions in writing to the Division

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• send sponsor final meeting minutes	DRUDP	1 month
• provide questions in an official submission	Wyeth-Ayerst	ASAP

Signature, minutes preparer

Addendum to Minutes: On April 23, 2001, Wyeth-Ayerst submitted a correspondence to the Division. This correspondence constituted their version of the minutes to the telephone conversation on April 16, 2001. This correspondence did not include a meeting request, the list of requested attendees, or a proposed time for a meeting. No questions were included for agency response. A new correspondence with questions should be submitted for review.

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

drafted: dm/4.26.01/N20527/S017TC4201

Concurrence:
T.Rumble 4.27.01

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Diane V. Moore
4/27/01 01:55:26 PM

APPEARS THIS WAY
ON ORIGINAL

Minutes of Teleconference

Date: April 11, 2001 **Time:** 2:35 PM– 3:00 PM **Location:** Parklawn; Room 17 B43

NDA: 20-527/S-017 **Drug Name:** (conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) tablets, 0.45 mg CE/1.5 mg MPA and 0.3 mg CEE/1.5mg MPA

Type of Meeting: Clinical Pharmacology and Biopharmaceutics Guidance

External Constituent: Wyeth-Ayerst Research

Meeting Chair: Dr. Ameeta Parekh

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Diane Moore – Regulatory Project Manager Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
David Lin, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

External Participants:
Joseph Sonk, Ph.D. - Senior Director, Therapeutic Area Head Women's Health, Worldwide Regulatory Affairs, Wyeth-Ayerst Laboratories
Nirdosh Jagota, Ph.D. – Director, Chemistry, Manufacturing and Quality Control, Wyeth-Ayerst

Background: Wyeth Ayerst sent the Division of Reproductive and Urologic Drug Products (DRUDP) a telefacsimilie dated April 11, 2001, regarding the MPA stability and dissolution specifications.

Meeting Objective:
To discuss the conjugated estrogens *in vitro* dissolution method and specifications.

Discussion Items:

- in the April 11, 2001, telefacsimilie, the sponsor has agreed to the 2-hour and 8-hour conjugated estrogens dissolution specifications, however, the sponsor's new proposed specifications for the 5-hour time-point is [redacted]
- on page 13 of the telefaxsimilie dated April 11, 2001, in the first paragraph of the response that begins, "Wyeth-Ayerst agrees to accept . . " there is error in the second sentence; the text states the NDA dissolution value of [redacted]) is now expressed as "Not more than [redacted] "; it should read "Not less [redacted] ; the specification page is correct

- **Decisions reached:**
- the Agency noted that based on the available clinical data, the 55-85% range is appropriate, therefore, the FDA proposed specifications are reasonable; in the future, after more data has been obtained with more batches, the sponsor can submit a prior approval supplement proposing revised specifications
- the sponsor will correct the error in the MPA dissolution value statement

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• send sponsor final meeting minutes	DRUDP	1 month

Signature, minutes preparer

Concurrence, Chair

Post Meeting Addendum:

- on April 12, 2001, Drs. Johnny Lau and Ameeta Parekh clarified with Dr. Joseph Sonk, at Wyeth-Ayerst Research, that the values in Tables 1 and 2 in the Pharmacokinetics section of the Prempro label should both be consistent (e.g., both arithmetic means); Dr. Joseph Sonk, from Wyeth-Ayerst Research, confirmed that the values in Table 1 of the current labeling are arithmetic means, but incorrectly labeled as geometric means
- the sponsor had removed the paragraph under [redacted]
- the sponsor proposed that the paragraph that begins, [redacted] could be substituted for the deleted paragraph because the data was from a prospectively designed study to address the dose proportionality of MPA over the labeled dose range

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

drafted: dm/4.12.01/N20527/S017TC412201

Concurrence:
T.Rumble, D.Lin, MRhee, J.Lau 4.12.01/A.Parekh 4.13.01

/s/

Diane V. Moore
4/13/01 11:13:26 AM

Ameeta Parekh
4/13/01 12:25:25 PM
I concur

APPEARS THIS WAY
ON ORIGINAL

Minutes of Teleconference

Date: April 10, 2001 **Time:** 11:30 AM– 12:00 PM **Location:** Parklawn; Room 17 B43

NDA: 20-527/S-017 **Drug Name:** (conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) tablets, 0.45 mg CE/1.5 mg MPA and 0.3 mg CEE/1.5mg MPA

Type of Meeting: Clinical Pharmacology and Biopharmaceutics Guidance

External Constituent: Wyeth-Ayerst Research

Meeting Chair: Dr. Ameeta Parekh

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Diane Moore – Regulatory Project Manager Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
David Lin, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

External Participants:
Chang Lee– Wyeth-Ayerst Laboratories
Nirdosh Jagota, Ph.D. – Director, Chemistry, Manufacturing and Quality Control, Wyeth-Ayerst
Robin Enever, Ph.D. - Vice President, Pharmaceutics and Process R&D, Wyeth-Ayerst Laboratories
John T. Carrano - Senior Director, Analytical Research & Development, Wyeth-Ayerst Laboratories

Background: The Division of Reproductive and Urologic Drug Products (DRUDP) sent Wyeth-Ayerst a letter dated April 4, 2001, outlining deficiencies in the Human Pharmacokinetics and Bioavailability section of the pending supplemental application for the 0.45 mg CE/1.5 mg MPA strength product.

Meeting Objective:
To discuss the medroxyprogesterone acetate (MPA) *in vitro* dissolution method and specifications.

Discussion Items:
- the Agency encourages the sponsor to use the *in vitro* dissolution apparatus to develop the MPA dissolution method
- the March 20, 1997, submission concerns the USP dissolution Apparatus 3 for the 0.625 mg CE/5.0 mg MPA and 0.625 mg CE/2.5 mg MPA oral tablets
- a Phase 4 commitment is needed for the sponsor to develop an MPA dissolution method for the combination 0.625 mg and 0.45 mg CE products using the dissolution apparatus rather than the disintegration apparatus

- the sponsor suggested the use of ' [redacted] (commercially available vessels with a dimple at the bottom) because the dissolution values using these vessels appear to be similar to the immediate dissolving product and values using the existing apparatus do not give meaningful dissolution values
- the use of [redacted] have been explored for lower doses of MPA; similar data with [redacted] for higher doses of MPA are needed
- the sponsor estimates that it will take four months to complete the preliminary results from the feasibility studies
- the 24-month stability data on 1.5 mg MPA was tested on Apparatus 3; the Division noted that Apparatus 3 is a disintegration apparatus, not a dissolution apparatus; the sponsor did not try Apparatus 1 or Apparatus 2 for 1.5 mg MPA
- following the USP acceptance table, a [redacted] means that all six tablets at Stage 1 cannot be less than [redacted] therefore, a specification of [redacted]) is acceptable
- because there is some inconsistency with some of the USP monographs, the sponsor is directed to reference Chapter 711 in the USP 24 for dissolution information (page 1943)

Decisions reached:

- the Agency requests more information, including preliminary *in vitro* dissolution results, for the higher doses of MPA from the combination products using a dissolution apparatus
- the sponsor agreed to send a proposal regarding the specifications for MPA to the Division in response to the April 4, 2001 letter
- the Division will have comments for the sponsor after review of the proposal and the data; the direction to proceed can be determined upon receipt of the Division's comments
- after determining the feasibility of the data, the sponsor will submit a commitment to test batches within a specific time frame in order to determine specifications for the MPA
- once the feasibility studies are completed, the time frame for the completion of the Phase 4 commitment can be decided; the Phase 4 commitment should include the conditions, specific data and a description of the method and data obtained from other equipment testing; the sponsor should provided data including the schematics and a diagram of the [redacted] apparatus
- the sponsor agreed to commit to perform the feasibility testing for dissolution methodology by four months post approval of the low dose (1.5 mg) MPA

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• submit response to April 4, 2001 letter	Wyeth-Ayerst	24 hours
• send sponsor final meeting minutes	DRUDP	1 month

Signature, minutes preparer

Concurrence, Chair

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

drafted: dm/4.10.01/N20527/S017TC410201

Concurrence:

J.Best, D.Lin, J.Lau, A.Parekh, M.Rhee 4.11.01

/s/

Diane V. Moore
4/11/01 05:24:52 PM

Ameeta Parekh
4/12/01 08:23:23 AM
I concur

APPEARS THIS WAY
ON ORIGINAL

Minutes of Teleconference

Date: April 5, 2001 **Time**: 10:30 – 11:00 AM **Location:** Parklawn; Room 17 B43

NDA: 20-527/S-017 **Drug Name**: (conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) tablets, 0.45 mg CE/1.5 mg MPA and 0.3 mg CEE/1.5mg MPA

NDA: 4-782/S-116 **Drug Name**: Premarin (conjugated estrogens) tablets, USP, 0.3 mg, 0.625 mg, 1.25 mg and 2.5 mg

Type of Meeting: Chemistry Guidance

External Constituent: Wyeth-Ayerst Research

Meeting Chair: Dr. David Lin

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Diane Moore – Regulatory Project Manager Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

External Participants:
Jennifer D. Norman – Associate Director, Worldwide Regulatory Affairs, Wyeth-Ayerst Laboratories
Nirdosh Jagota, Ph.D. – Director, Chemistry, Manufacturing and Quality Control, Wyeth-Ayerst

Background: The 1995 Phase 4 commitment regarding the marketing of cycle packs of Prempro 0.625 mg CE/2.5 mg MPA and 0.625 mg CE/5.0 mg MPA tablets containing MPA supplied by [redacted] stated that these tablets would not be marketed until 1-year stability data on three batches of combination tablets for each regimen (each batch using a different lot of [redacted]) was provided to the Agency in a post approval supplement. A February 16, 1999, annual report indicated that the data was being generated.

Meeting Objective:
To discuss the stability data for the 0.45 mg CE/1.5 mg MPA tablet containing [redacted]

Discussion Items:
Prempro NDA 20-527/S-017

- only one batch with [redacted] was submitted to the efficacy supplement; this is inconsistent with the Agency's policy
- the Agency proposes that the data for the previous Phase 4 commitment for the 0.625 mg Prempro tablet be combined with the new 0.45 mg CE/1.5 mg MPA dose Prempro tablet into a new Phase 4 commitment to submit stability data from three batches of all strengths of Prempro tablets in an annual report; in the interim, [redacted] material can be used
- a time-frame for the completion of data and data submission must be included in the commitment letter

Premarin Supplement 116

- the sponsor stated that the use of sinker weights strongly supports the conclusion that the variability of dissolution results in the quality control testing is reduced; however, the FDA statistical analysis of the data using sinker weights concluded that this conclusion is too strong; the method using sinker weights provides at least equivalent variability to the method without sinker weights

Decisions reached:

- the conclusions given by the sponsor must be modified to indicate that the method using sinker weights results in equal means and at least equal variability to the method without using sinker weights

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• send sponsor final meeting minutes	DRUDP	1 month

Signature, minutes preparer

Concurrence, Chair

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

drafted: dm/4.6.01/N20527/S017TC4201

Concurrence:
J.Best, D.Lin 4.9.01

APPEARS THIS WAY
ON ORIGINAL

/s/

Diane V. Moore
4/11/01 12:28:21 PM

David T. Lin
4/11/01 12:38:32 PM
I concur.

APPEARS THIS WAY
ON ORIGINAL

Minutes of Teleconference

Date: April 2, 2001 **Time**: 4:00 - 4:10 PM **Location**: Parklawn; Room 17 B43

NDA: 20-527/S-017 **Drug Name**: (conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) tablets, 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA

Type of Meeting: Clinical Guidance

External Constituent: Wyeth-Ayerst Research

Meeting Chair: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Shelley Slaughter, M.D., Ph.D. – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., – Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Joseph Sonk, Ph.D. - Senior Director, Therapeutic Area Head Women's Health, Worldwide Regulatory Affairs, Wyeth-Ayerst Laboratories
Jennifer D. Norman – Associate Director, Worldwide Regulatory Affairs, Wyeth-Ayerst Laboratories

Background: On March 30, 2001, the Division discussed clinical concerns regarding the 0.3 mg CE/1.5 mg MPA dosage strength tablet. This is a follow-up discussion.

Meeting Objective:
To discuss the sponsor's logistical concerns regarding removal of the 0.3 mg CE/1.5 mg MPA dosage strength from the supplemental NDA application

Discussion Items:

- data submitted to the supplement from the ongoing trial is preliminary data; additional data will be submitted at the completion of the study; the sponsor is concerned that the interim information regarding the [redacted]
- the Freedom of Information (FOI) section of the Agency normally redacts information for non-approved and withdrawn doses; the Division cannot guarantee that the FOI section would redact everything in reference to the 0.3 mg CE/1.5 mg MPA dose
- the sponsor requested the same consideration that was given to [redacted] by the Freedom of Information section following non-approval of their [redacted] in their NDA

Decisions reached:

- references to safety with the 0.3 mg CE /1.5 mg MPA dosage strength will be included in the Division reviews; references to efficacy will be removed
- the clinical review of a withdrawn dosage strength would list breast cancers for safety; the clinical review would not discuss the benefit/risk assessment of the withdrawn
- the sponsor

Action Items:

• **Item:**	**Responsible Person**:	**Due Date**:
• send sponsor final meeting minutes	DRUDP	1 month
	Wyeth-Ayerst	1-2 days

Signature, minutes preparer

Concurrence, Chair

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

drafted: dm/4.6.01/N20527/S017TC4201

Concurrence:
J.Best, T.van der Vlugt 4.9.01

APPEARS THIS WAY ON ORIGINAL

/s/

Diane V. Moore
4/12/01 11:34:57 AM
For Dr. Shelley Slaughter

Ridgely C. Bennett
4/12/01 12:42:14 PM

APPEARS THIS WAY
ON ORIGINAL

Minutes of Teleconference

Date: March 30, 2001 **Time**: 3:00 - 3:30 PM **Location:** Parklawn; Room 17 B43

NDA: 20-527/S-017 **Drug Name**: (conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) tablets, 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA

Type of Meeting: Clinical Guidance

External Constituent: Wyeth-Ayerst Research

Meeting Chair: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Shelley Slaughter, M.D., Ph.D. – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Participants:
Joseph Sonk, Ph.D. - Senior Director, Therapeutic Area Head Women's Health, Worldwide Regulatory Affairs, Wyeth-Ayerst Laboratories
Jennifer D. Norman – Associate Director, Worldwide Regulatory Affairs, Wyeth-Ayerst Laboratories
Cynthia Davidson – Worldwide Regulatory Affairs

Background: On March 27, 2001, in a voice-mail message, the Division requested Wyeth-Ayerst to explain a discrepancy found between the original submitted data and data submitted in an amendment dated March 7, 2001, in Group G (the original submission listed 32 subjects in Group G while the March 7, 2001, submission listed 33 subjects in Group G).

Meeting Objective:
To discuss clinical concerns regarding Supplement 17.

Discussion Items:
- data from the post-database lock revises the adverse events (AE) table in the NDA submission for only the treatment emergent adverse effects; the percentages are changed because anxiety has been added as a new category; the sponsor will send a telefacsimilie to the medical reviewer for her convenience in addition to an official submission
- the explanation to the discrepancy in the number of subjects in Group G in the Tables of Mean Number of moderate-to-severe vasomotor symptoms (MSVS) and Mean Severity of MSVS was submitted to the Agency on March 22, 2001 (32 patients were listed in the original study, but 33 patients were in the March 7, 2001, submission); one patient in the study who did not have Week 1 data was not included in the table in the original submission; that patient was included in the data in the March 7, 2001, submission because the data in the table listed patients using last observation

carried forward (LOCF); using that criteria, the patient had data that allowed her to be included in the analysis

- the Division has some concerns regarding the 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate strength
  - overall, the 0.3 mg CE/1.5 mg MPA is the lowest effective dose; there are concerns regarding the efficacy of the 0.3 mg CE/1.5 mg MPA dose for the subgroup of women close to menopause (under 50 years of age)
  - there are concerns regarding the number of breast cancers found in the 0.3 mg CE/1.5 mg MPA arm in comparison with the other arms of the study
  - there is a less favorable lipid profile for the 0.3 mg CE/1.5 mg MPA arm in comparison with other doses studied
  - the Division offered some options that the sponsor might wish to consider for the 0.3 mg CE/1.5 mg MPA dosage strength
    - potentially, —
    - the Year 2 data from the ongoing trial would provide additional safety data for the 0.3 mg CE/1.5 mg MPA dosage strength
    - the sponsor could withdraw the 0.3 mg CE/1.5 mg MPA strength and resubmit at a later date when additional data has been obtained

Decisions reached:

- the sponsor will respond on Monday to the suggestions from the Division
- the sponsor requested that a teleconference be scheduled on Monday between the DRUDP Medical Officer and Team Leader and the main study investigator for this study at Wyeth-Ayerst, Dr. Jim Picar

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• schedule telecon between Wyeth Ayerst and DRUDP Medical Officer	Ms. Moore	April 2, 2001
• Inform DRUDP if a withdrawal is desired for 0.3 mg CE/1.5 mg MPA strength	Wyeth-Ayerst	April 2, 2001

Signature. minutes preparer

Concurrence, Chair

Post meeting addendum: On March 31, 2001, Jennifer Norman, of Wyeth-Ayerst called Diane Moore, DRUDP Project Manager, and informed her that the requested teleconference between the Wyeth-Ayerst study investigator and the DRUDP Medical Officer and Team Leader would not be necessary. No teleconference was scheduled.

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

drafted: dm/3.31.01/N20527/S017TC33001

Concurrence:.

J.Best, T.van der Vlugt 4.2.01/S.Slaughter 4.6.01

/s/

Diane V. Moore
4/10/01 07:56:41 PM
For Shelley Slaughter

Ridgely C. Bennett
4/11/01 10:23:30 AM

APPEARS THIS WAY
ON ORIGINAL

Minutes of Teleconference

Date: March 9, 2001 **Time**: 4:00 - 4:05 PM **Location:** Parklawn; Dr. van der Vlugt's Office

NDA: 20-527/S-017 **Drug Name**: (conjugated equine estrogens (CEE)/medroxyprogesterone acetate (MPA) tablets, 0.45 mg CEE/1.5 mg MPA and 0.3 mg CEE/1.5mg MPA

Type of Meeting: Statistical Guidance

External Constituent: Wyeth-Ayerst Research

Meeting Chair: Dr. Theresa van der Vlugt

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

External Participants:
Jennifer D. Norman – Associate Director, Worldwide Regulatory Affairs, Wyeth-Ayerst Laboratories
Bob Northington, Ph.D. – Statistician, Wyeth-Ayerst Laboratories

Meeting Objective:
To discuss the FDA request for additional data for Supplement-017.

Background: Results from Study 309 need to be recalculated to support the indication for the treatment of moderate-to-severe vasomotor symptoms (MSVS).

Discussion Items:
- the Division intends to focus on the patients who met the inclusion criteria at baseline of at least 7-8 MSVS per day or at least 50 MSVS in the seven days prior to randomization
- the intent-to-treat (ITT) analysis of the Efficacy Evaluable (EE) population is needed to complete the review
- the ITT analysis of the EE population should use the last visit carried forward (LVCF) for weeks with missing data
- the results of the covariate-adjusted analysis reported in the supplement most likely will be the same as the results of the ANOVA of actual change from baseline
- the Division requests a table displaying the mean number of MSVS at baseline, Weeks, 4, 8, and 12 and the mean change from baseline for Weeks 4, 8 and 12; last visit carried forward (LVCF) should be used for this table
- the Division also requests a similar table for severity of MSVS

Decisions reached:

- the sponsor will submit the requested tables to the supplemental application

Action Items:

• **Item:**	**Responsible Person**:	**Due Date**:
• submit requested tables	Wyeth-Ayerst	1-week

Signature, minutes preparer

Concurrence, Chair

drafted: dm/3.9.01/N20527S017TC3901

Concurrence:
T.Rumble, T.van der Vlugt 3.19.01/L.Kammerman 4.3.01

/s/

Diane V. Moore
4/3/01 12:49:33 PM

Theresa Van Der Vlugt
4/6/01 10:34:43 AM

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: March 5, 2001 **Time**: 10:30 - 11:30 AM **Location:** Parklawn; Room 17 B43

NDA: 20-527/S-017 **Drug Name**: (conjugated equine estrogens (CEE)/medroxyprogesterone acetate (MPA) tablets, 0.45 mg CEE/1.5 mg MPA and 0.3 mg CEE/1.5mg MPA

Type of Meeting: Labeling/9-month status meeting

Indications: Treatment of moderate-to-severe vasomotor symptoms (MSVS) — vulvar and vaginal atrophy (VVA)

Sponsor: Wyeth-Ayerst Research

Meeting Chair: Ms. Diane Moore

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objective:
To discuss the labeling for Supplement-017.

Background: The goal date for completed reviews is March 16, 2001. The action package will be circulated beginning March 23, 2001. The Division goal date is April 15, 2001

Discussion Items:
- Clinical
  - review pending; additional data recalculations have been requested for the VMS and VVA indications
  - adding 1.5 mg MPA does not impact the 0.3 mg estrogen dose for efficacy in VVA for the endometrium protection claim; the MPA arms have incidence rates of 1% or less for endometrial hyperplasia; one case of hyperplasia in the 0.45 mg CEE/1.5 mg MPA arm is being reclassified as carcinoma in a polyp (1 of 272)

- CMC
  - review pending; the review may be delayed because the manufacturing site report has not been finalized; the Puerto Rico manufacturing site may receive a warning letter; a hold recommendation is possible; the Team-Leader notes on the chemistry review will be incorporated in the Deputy Director memorandum for the supplement
  - revisions to the storage statement have been incorporated into the proposed labeling on the "N" drive
  - additional stability data, sterility and dissolution data have been requested; they are due March 9, 2001
- Tradename
  - the Division prefers that the two new lower estrogen doses utilize the tradename "Prempro"; the respective dosage strengths would be designated by writing the doses for both the estrogen and progestin components on prescriptions for all strengths; a label will be submitted to the sponsor that incorporates all Prempro doses in the same label; the Division finds the proposed trademark [redacted] unacceptable
- Clinical Pharmacology and Biopharmaceutics
  - review pending
  - *in-vitro* dissolution data for the white clinical lots (tablets) and the colored to-be-marketed lots (tablets) were received; although different time-points (but the same methods) were used for the clinical and to-be-marketed batches, the curves are similar when superimposed and support the similarity of the two formulations
  - the Biopharmaceutics briefing is scheduled for March 19, 2001

Decisions reached:
- the reviewers should add their labeling revisions to the label on the Division "N" drive when available

Action Items:

• **Item:**	**Responsible Person**:	**Due Date**:
• update label on N: drive	all reviewers	March 16, 2001

Signature, minutes preparer

Concurrence, Chair

drafted: dm/3.15.01/N20527S0173501

Concurrence:
T.Rumble, T.van der Vlugt 3.19.01/J.Lau, A.Parekh 3.28.01/D.Lin 3.29.01
Response not received from L.Kammerman

APPEARS THIS WAY
ON ORIGINAL

/s/

Diane V. Moore
3/29/01 12:46:24 PM

APPEARS THIS WAY
ON ORIGINAL

Minutes of Teleconference

Date: March 9, 2001 **Time**: 4:00 - 4:05 PM **Location:** Parklawn; Dr. van der Vlugt's Office

NDA: 20-527/S-017 **Drug Name**: (conjugated equine estrogens (CEE)/medroxyprogesterone acetate (MPA) tablets, 0.45 mg CEE/1.5 mg MPA and 0.3 mg CEE/1.5mg MPA

Type of Meeting: Statistical Guidance

External Constituent: Wyeth-Ayerst Research

Meeting Chair: Dr. Theresa van der Vlugt

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

External Participants:
Jennifer D. Norman – Associate Director, Worldwide Regulatory Affairs, Wyeth-Ayerst Laboratories
Bob Northington, Ph.D. – Statistician, Wyeth-Ayerst Laboratories

Meeting Objective:
To discuss the FDA request for additional data for Supplement-017.

Background: Results from Study 309 need to be recalculated to support the indication for the treatment of moderate-to-severe vasomotor symptoms (MSVS).

Discussion Items:
- the Division intends to focus on the patients who met the inclusion criteria at baseline of at least 7-8 MSVS per day or at least 50 MSVS in the seven days prior to randomization
- the intent-to-treat (ITT) analysis of the Efficacy Evaluable (EE) population is needed to complete the review
- the ITT analysis of the EE population should use the last visit carried forward (LVCF) for weeks with missing data
- the results of the covariate-adjusted analysis reported in the supplement most likely will be the same as the results of the ANOVA of actual change from baseline
- the Division requests a table displaying the mean number of MSVS at baseline, Weeks, 4, 8, and 12 and the mean change from baseline for Weeks 4, 8 and 12; last visit carried forward (LVCF) should be used for this table
- the Division also requests a similar table for severity of MSVS

Decisions reached:

- the sponsor will submit the requested tables to the supplemental application

Action Items:

• **Item:**	**Responsible Person**:	**Due Date**:
• submit requested tables	Wyeth-Ayerst	1-week

Signature, minutes preparer

Concurrence, Chair

drafted: dm/3.9.01/N20527S017TC3901

Concurrence:
T.Rumble, T.van der Vlugt 3.19.01/L.Kammerman 4.3.01

APPEARS THIS WAY
ON ORIGINAL

/s/

Diane V. Moore
4/3/01 12:49:33 PM

Theresa Van Der Vlugt
4/6/01 10:34:43 AM

APPEARS THIS WAY
ON ORIGINAL

/s/

Diane V. Moore
3/29/01 12:46:24 PM

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: February 13, 2001 **Time**: 1:00 - 1:45 PM **Location:** Parklawn; Room 17 B43

NDA: 20-527/S-017 **Drug Name**: (conjugated equine estrogens (CEE)/medroxyprogesterone acetate (MPA) tablets, 0.45 mg CEE/1.5 mg MPA and 0.3 mg CEE/1.5mg MPA

Type of Meeting: Labeling/Status meeting

Sponsor: Wyeth-Ayerst Research

Meeting Chair: Dr. Daniel Shames

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Daniel Shames, M.D. – Deputy Director, DRUDP (HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Meeting Objective:
To discuss the labeling for Supplement 17.

Background: The goal date for completed reviews to be given to NDA team leader is March 16, 2001. The action package will be circulated beginning March 23, 2001. The Division goal date is April 5, 2001

Discussion Items:
- Clinical
  - review pending; both low doses are effective for VMS and VVA
- CMC
  - the EES inspection has been performed, however, the report has not been completed
  - the storage statement that reads " [redacted] should be updated to read **"Store at controlled room temperature 25°C"**
  - additional stability data are needed; sterility and dissolution data should be requested
  - the sponsor's proposal to add a new trademark [redacted]) to the two lowest doses will be discussed with the Office (OPDRA has reviewed the tradename and found it to be unacceptable)
- Clinical Pharmacology and Biopharmaceutics
  - review pending

- additional dissolution information is needed; a full profile should be submitted with multiple time points to substantiate the similarity between the white clinical lots (tablets) and the colored to-be-marketed lots (tablets)

Decisions reached:

- Regulatory
  - labeling will not be sent to the sponsor until the trademark issue has been decided

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• discuss tradename with Office with a copy of the labeling	Dr. Shames	1-2 weeks
• request dissolution data for clinical and to-be-marketed lots	Ms. Moore	1 week

Signature, minutes preparer

Concurrence, Chair

drafted: dm/2.24.01/N20527S017SM21301

Concurrence:
T.Rumble 2.28.01/. van der Vlugt 3.1.01/D.Lin 3.8.01/J.Lau, D.Shames 3.10.01
S.Slaughter 3.19.01
Response not received from and A.Parekh

/s/

Diane V. Moore
3/19/01 04:10:32 PM

Daniel A. Shames
3/20/01 09:26:15 AM

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: January 25, 2001 **Time**: 12:45 - 2:15 PM **Location:** Parklawn; Room 17 B43

NDA: 20-527/S-017 **Drug Name**: (conjugated equine estrogens (CEE)/medroxyprogesterone acetate (MPA) tablets, 0.45 mg CEE/1.5 mg MPA and 0.3 mg CEE/1.5mg MPA

Type of Meeting: Labeling/Status meeting

Sponsor: Wyeth-Ayerst Research

Meeting Chair: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Shelley Slaughter, M.D., Ph.D. – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Meeting Objective:
To discuss the labeling for Supplement 17.

Background: The Division goal date is March 16, 2001.

Discussion Items:
- the clinical reviewer has made revisions to the proposed labeling (see attached)
- the sponsor is not proposing changes in the dissolution specifications for Prempro Premphase
- the CMC review has not been completed; the reviewer will note any chemistry revisions in the labeling
- Clinical Pharmacology and Biopharmacology review is pending

Decisions reached:
- OPDRA should be invited to the next labeling meeting

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• invite OPDRA to next meeting and supply attendees with a copy of the labeling	Ms. Moore and	1-2 weeks
• confer with Dr. Price as to whether other HRT labels have graphs on endometrial bleeding	Dr. van der Vlugt	1-2 weeks
• request completion date for analyses on HOPE study from Wyeth-Ayerst	Ms. Moore	1-2 weeks
• request blister samples from sponsor	Ms. Moore	1-2 weeks

- send copy of label to Deputy Director for comment Ms. Moore 1-2 weeks
- request location of letters of authorization in IND from sponsor Ms. Moore 1-2 weeks

Signature, minutes preparer

Concurrence, Chair

Post-meeting Addendum: Blister samples and letters of authorization were requested from the sponsor on January 26, 2001. The sponsor estimated that the completion date for the analyses of the HOPE study would be submitted in May or June of 2001.

drafted: dm/1.29.01/N20527/S-017SM12501

Concurrence:
T.Rumble 1.30.01/D.Lin 1.30.01/T.van der Vlugt 1.31.01/S.Slaughter 2.12.01/J.Lau 2.22.01
cc:
NDA Arch:
HFD-580/Div File
HFD-580/SAllen/DShames/SSlaughter/Tvander Vlugt/TRumble/LKammerman/JLau/AParekh
HFD-580/DLin/MRhee

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 34

Draft Labeling
(not releasable

/s/

Diane V. Moore
2/22/01 09:22:48 PM

Shelley Slaughter
2/27/01 12:54:01 PM

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: January 2, 2001 **Time**: 1:00 - 1:40 PM **Location:** Parklawn; Room 17 B43

NDA: 20-527/S-017 **Drug Name**: (conjugated equine estrogens (CEE)/medroxyprogesterone acetate (MPA) tablets, 0.45 CEE/1.5 MPA and 0.3 CEE/1.5mg MPA

Type of Meeting: 7-month Status

Sponsor: Wyeth-Ayerst Research

Meeting Chair: Dr. Daniel Shames

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Daniel Shames, M.D. – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objective:
To discuss the status of Supplement 17 that proposes two new lower doses for the treatment of moderate to severe vasomotor symptoms associated with the menopause and the [redacted] vulvar and vaginal atrophy. The supplement incorporated a continuous, combined regimen.

Background: The primary goal date is April 15, 2001. The secondary goal date is June 15, 2001.

Decisions reached:
- Regulatory
  - additional requested financial disclosure information has been received; PK data in ASCI format and annotated labeling have been requested
  - the goal date for completion of all primary reviews, including Team Leader sign-off is March 16, 2001
- Pharmacology
  - since higher doses of these ingredients have been approved, Pharmacology has no toxicological concerns
- Tradename
  - the sponsor proposed the new tradename [redacted] for these lower doses; the Office of Postmarketing Drug Risk Assessment (OPDRA) objects to the new name on the grounds that only one tradename should be allowed per sponsor for the same ingredients; a Center policy is being developed to address this issue
- Clinical
  - review pending
  - one center did not adhere to Good Clinical Practices; that site was excluded from the study

- DSI
  - no inspections have been requested for this supplement because both drug substances are approved drug substances for the intended indications; this study was conducted as a Phase 4 commitment at the time of the Prempro approval; no significant differences in study demographics and outcomes were observed between the individual participating study centers; the one investigator financial disclosure that was questioned involved a center with a small number of enrolled subjects for which a DSI inspection was not warranted
- Chemistry, Manufacturing and Quality Control
  - review pending with no concerns noted at this point
  - ——
- Clinical Pharmacology and Biopharmaceutics
  - review pending with no comments at this time
- Statistical
  - a discussion of this NDA with the Medical Officer and statisticians has been scheduled for January 3 to review the submission and discuss clinical concerns
  - review pending; maturation indexes need to be addressed in the review

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• discuss tradename issue with Dr. Jerry Phillips	Ms. Moore and Dr. van der Vlugt	1-2 weeks
• determine if pre-printed scripts can be required	Ms. Moore	1 week
• schedule labeling meeting for third week in January	Ms. Moore	1 week

Signature, minutes preparer

Concurrence, Chair

Post Meeting Addendum:

- the manufacturing sites have been inspected and inspections are current; final results pending
- Dr. van der Vlugt and Ms. Moore contacted Dr. Jerry Phillips on January 3, 2001, and discussed the tradename issue. A Center policy is being developed. Currently, OPDRA's recommends not allowing more than one tradename for the same ingredients per sponsor.
- there is no regulation that allows the Agency to require pre-printed scripts for a drug, although the use of pre-printed scripts is available to the sponsor if desired

drafted: dm/1.9.01/N20527/S-017SM1201

Concurrence:
T.Rumble, D.Shames, L.Kammerman 1.10.01T.van der Vlugt, SSlaughter 1.11.01

cc:
NDA Arch:
HFD-580 Div File
HFD-580 SAllen/DShames/SSlaughter/Tvander Vlugt/TRumble/LKammerman/JLau/AParekh
HFD-580 DLin/MRhee

/s/

Diane V. Moore
1/26/01 11:12:12 AM

Daniel A. Shames
1/26/01 03:29:31 PM

APPEARS THIS WAY
ON ORIGINAL

Addendum to August 1, 2000 Meeting Minutes

Background: The August 1, 2000, meeting minutes noted that the submitted labeling did not include annotated references; annotated labeling was to be requested.

Comment: The original submission did have annotated references in the way of footnotes at the end of the labeling section; no additional annotated references were requested.

Diane Moore, PM

/s/

Diane V. Moore
4/6/01 08:54:38 AM

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: August 1, 2000 **Time:** 12:00 - 12:30 AM **Location:** Parklawn; Room 17 B43

NDA: 20-527/S-017 **Drug Name:** (conjugated estrogens (CEE)/medroxyprogesterone acetate (MPA) tablets, 0.45 CEE/1.5 MPA and 0.3 CEE/1.5mg MPA

Type of Meeting: Filing

Sponsor: Wyeth-Ayerst Research

Meeting Chair: Dr. Susan Allen

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Susan Allen, M.D., M.P.H. – Acting Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)
Daniel Shames, M.D. – Acting Deputy Director, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Meeting Objective:
To discuss the fileability of Supplement 17 for two new lower doses for the treatment of moderate to severe vasomotor symptoms associated with the menopause and the —— vulvar and vaginal atrophy.

Background: The primary goal date is April 15, 2001. The secondary goal date is June 15, 2001.

Decisions reached:
- Regulatory
  - fileable
  - financial disclosure was made on only 50% of the investigators in the original submission; additional financial disclosure information has been requested
- Pharmacology
  - fileable; since both the CEE and MPA drugs have been approved in higher doses, Pharmacology has no objections to filing

- Tradename .
  - the sponsor proposes to [redacted]
- Clinical
  - fileable
  - the sponsor has a Phase 4 commitment dated December 1994 in which they are to establish a minimum effective dose for the prevention of osteoporosis; the HOPE study is underway to address this commitment; this supplement is not meant to satisfy that commitment
  - there appears to be a large variability in study center enrollment (see Medical Officer Review)
- DSI
  - at this time, it is known that [redacted], only a small number of patients were enrolled at that site; a DSI inspection does not appear to be warranted for that site at this time
- Chemistry, Manufacturing and Quality Control
  - fileable
  - there has been no change from the approved drug substance
  - the Drug Master File (DMF) needs to be updated (last update was 1996)
  - the sponsor is requesting a 2-year expiration date
  - the sponsor requested a categorical exclusion for the environmental assessment
- Clinical Pharmacology and Biopharmaceutics
  - fileable
  - the proposed dissolution method and data are different from the USP method; the proposed in vitro dissolution method and specifications should be submitted
  - the tablets used in the clinical trials is different from the to-be-marketed tablets; data, such as *in-vitro* dissolution data, should be submitted to demonstrate that there is no difference between the two formulations
  - the submitted labeling does not include annotated references; annotated labeling should be submitted
  - the Biopharmaceutics reviewer requests pharmacokinetic data be provided in ASCI format
- Statistical
  - fileable
  - issues to be addressed during review

Action Items:

Item:	**Responsible Person:**	**Due Date:**
discuss tradename issue with Dr. Jerry Phillips	Ms. Moore	1-2 weeks
request PK data in ASCI format	Ms. Moore	1 week
request annotated labeling	Ms. Moore	1 week
request update to [redacted]	Dr. Lin	during review

/S/ 9/18/00
Signature, minutes preparer

/S/ 9/19/00
Concurrence, Chair

drafted: dm/8.14.00/N20527/S-017FM8100

Concurrence:
MRhee, SAllen 8.21.00/Tvan der Vlugt 8.22.00/DLin 8.23.00/TRumble 8.24.00

Responses not received from SSlaughter, DShames, AParekh, VJarugula, JLau

cc:
NDA Arch:
HFD-580/Div File
HFD-580/SAllen/DShames/SSlaughter/Tvander Vlugt/TRumble/LKammerman/JLau/AParekh
HFD-580/DLin/MRhee/VJarugula

APPEARS THIS WAY
ON ORIGINAL

Division of Reproductive and Urologic Drug Products

ADMINISTRATIVE REVIEW OF APPLICATION

Application Number: **NDA 20-527/S-017**

Name of Drug: Conjugated Estrogens and Medroxyprogesterone Acetate Combination Tablets (0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA)

Sponsor: **Wyeth-Ayerst Laboratories**

Material Reviewed: **NDA volumes**

Submission Date: **June 15, 2000**

Receipt Date: **June 15, 2000**

Filing Date: **August 14, 2000**

User-Fee Goal Date(s): **April 15, 2000**

Proposed Indication: **treatment of moderate to severe vasomotor symptoms associated with menopause and [redacted] vulvar and vaginal atrophy**

Other Background Information:

Review

PART I: OVERALL FORMATTING[a]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Cover Letter (original signature)	X		Vol. 1.1
2. Form FDA 356h (original signature)	X		Vol. 1.1
a. Reference to DMF(s) & Other Applications		X	
3. Patent information & certification	X		Vol. 1.1, Pages 26 and 27
4. Debarment certification (note: must have a definitive statement)	X		Vol. 1.1, Page 29

5. Financial Disclosure	X		Vol. 1.1, Page 32
6. Comprehensive Index	X		Vol. 1.1, Page 6
7. Pagination	X		
8. Summary Volume	X		Vol. 3
9. Review Volumes	X		
10. Labeling (PI, container, & carton labels)	X		Vol.2, Pages 2-40.
a. unannotated PI	X		Vol. 2, Pages 2-30
b. annotated PI		X	
c. immediate container	X		Vol. 2, Pages 30, 32, 33, 34, 35, 37, 38, 39, 40
d. carton	X		Vol. 2, Pages 31, 36
e. foreign labeling (English translation)		X	
11. Foreign Marketing History		X	
12. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		electronic CRTs ITEMS 11 and 12
13. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		electronic CRTs ITEMS 11 and 12

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		Vol. 19, Page 5
2. Summary of Each Technical Section			
a. Chemistry, Manufacturing, & Controls (CMC)	X		Item 3, Vol. 3, Page 31
b. Nonclinical Pharmacology/Toxicology	X		Vol. 19, Page 5-17
c. Human Pharmacokinetic & Bioavailability	X		Item 3, Vol. 3, Page 66
d. Microbiology		X	N/A
e. Clinical Data & Results of Statistical Analysis	X		Item 3, Vol. 3, Page 68
3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		Item 3, Vol. 3, Page 177 Pg 304 vol 70 study 309-US
4. Summary of Safety	X		Vol. 53, page 134
5. Summary of Efficacy	X		Vol. 53, Page 90

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. List of Investigators	X		Item 19, page 32
2. Controlled Clinical Studies			
a. Table of all studies	X		Vol. 71, Page 12
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		Vol. 70, Page 296
c. Optional overall summary & evaluation of data from controlled clinical studies	X		Vol. 53. page 3-8
3. Integrated Summary of Efficacy (ISE)		X	N/A only one study submitted
4. Integrated Summary of Safety (ISS)		X	N/A only one study submitted
5. Drug Abuse & Overdosage Information	X		Vol. 7, Page 303
6. Integrated Summary of Benefits & Risks of the Drug	X		Vol. 70, Page 304
7. Gender/Race/Age Safety & Efficacy Analysis Studies	X	X	Gender: N/A (only used in women) Age: Vol. 53, (Tables 26 through 28; page 1592), Text page 98 Ethnic Origin: Vol. 53, (Tables 29 through 32; page 2027, Text page 100

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		X	Waiver requested
2. Diskettes			
a. Proposed unannotated labeling in MS WORD 8.0	X		(see review aid)
b. Stability data in SAS data set format		X	not requested by FDA reviewer
c. Efficacy data in SAS data set format	X		
d. Biopharmacological information & study summaries in MS WORD 8.0	X		(see review aid)
e. Animal tumorigenicity study data in SAS data set format		X	N/A new dose for approved application
3. User-fee payment receipt	X		Item 18 Page 31

Y=Yes (Present), N=No (Absent)

[a] GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS (FEBRUARY 1987).

[b] GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS (FEBRUARY 1987).

[c] GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS (JULY 1988).

Additional Comments:

Conclusions: Fileable

/S/ 6/21/00
Regulatory Health Project Manager

/S/ 6/22/00
Concurrence

cc:
Original NDA
HFD-580/Div. Files
HFD-580/PM/
HFD-580/Allen/Mann
HFD-%80/Reviewers
draft:
r/d Initials:
final:

ADMINISTRATIVE REVIEW

APPEARS THIS WAY ON ORIGINAL

Filing Memorandum
Division of Reproductive and Urologic Drug Products

sNDA 20-527

Trade Name:	No tradename provided
Generic Name:	Conjugated equine estrogens (CEE) Medroxyprogesterone acetate (MPA)
Sponsor:	Wyeth-Ayerst Research P.O. Box 8299 Philadelphia, PA 19101-8299
Submission Date:	June 15, 2000
Date Received:	June 15, 2000
Indications:	• Treatment of moderate to severe vasomotor symptoms associated with the menopause. • [redacted] vulvar and vaginal atrophy.
Dose form:	Tablet
Treatment Schedule:	Continuous for 28 days
Dosage Regimen:	• 0.45 mg CEE plus 1.5 mg MPA • 0.30 mg CEE plus 1.5 mg MPA
User Fee Goal Date:	April 15, 2000
Division Goal Date:	March 15, 2000
Filing Date:	August 14, 2000
Medical Reviewer:	Theresa H. van der Vlugt, M.D., M.P.H.

Submission Resume

In this submission, Wyeth-Ayerst proposes two lower doses of continuous conjugated equine estrogens plus medroxyprogesterone acetate for the treatment of moderate-to-severe vasomotor symptoms [redacted] vulvar and vaginal atrophy associated with the menopause. The two dosage regimens are 0.45 mg CEE plus 1.5 mg MPA and 0.30 mg CEE plus 1.5 mg MPA.

The clinical trial conducted and continuing, Study 0713D2-309-US (the HOPE Study), was undertaken to satisfy a post-approval commitment to the FDA for Prempro™ 2.5 (approved 1994) to determine the lowest effective dose of CEE/MPA for the prevention of osteoporosis. This 8 arm, 24-month, double-dummy clinical trial includes 2,673 postmenopausal women who received one of the 4 following doses of CEE plus MPA: 0.625 mg/2.5 mg MPA, 0.45 mg CEE/2.5 mg MPA, 0.45 mg CEE/1.5 mg MPA, and 0.30 CEE/1.5 mg MPA; the corresponding doses of CEE alone (0.625 mg, 0.45 mg, and 0.30 mg); and placebo. Subjects were randomly assigned doses and were instructed to take 2 tablets of the study medication daily (one active tablet and one matching placebo tablet or two matching placebo tablets) and one [redacted] tablet daily at approximately the same time each day. The Hope Study is comprised of a basic study (12 months, 13 cycles) and a metabolic/osteoporosis substudy (24 months, 26 cycles).

The Sponsor submitted a plan for an interim analysis of the HOPE Study data at 1-year to the Division. On December 9, 1999 the Sponsor was notified that the proposed statistical plan for an interim analysis was appropriate and that appropriate precautions were being taken to assure that the study blind was maintained for the osteoporosis and metabolism substudy.

The 12-month data from completed study year 1 (2153 subjects, 1,553 subjects in the basic study and 599 subjects ongoing in the metabolic/osteoporosis substudy) submitted in this sNDA application supports the safety and efficacy of the doses in reducing the incidence of estrogen-associated endometrial hyperplasia and in relieving moderate-to-severe hot flushes and vulvar and vaginal atrophy. The Sponsor anticipates submitting the full 2-year study data for a prevention of osteoporosis indication.

The primary efficacy measurement for study year 1 is an assessment of the incidence of endometrial hyperplasia, made by endometrial biopsies conducted at baseline, 6 months and 12 months. Vasomotor symptoms and vaginal maturation indexes, assessed by evaluation of daily diaries and vaginal cytology smears, are secondary efficacy measurements.

Two completed comparative bioavailability studies are also included in the sNDA application.

Fileability of Supplemental NDA 20-527/S-017

Supplemental NDA 20-527/S-017 is fileable.

Review Issues

1) Large variability in study center enrollment (57 of 58 centers enrolled from 3 to 147 subjects; 1 center (Center 30952) was found by the Sponsor not to be in compliance with Good Clinical Practice (GCP) leading to early termination of the study site and exclusion of all data from this site.
2) Patients were enrolled in the study if they had a serum estradiol concentration of ≤ 184 pmol/L (equivalent to ≤ 50 pg/ml), FSH concentration of ≥ 30 IU/L
3) Absence of baseline inclusion criteria for 7-8 moderate-to-severe hot flushes per day or 50-60 per week (MSVS substudy population represents only 9% of the total study population (240/2673)
4) An analysis of the change from baseline for the frequency and severity of hot flushes was not performed. Instead, the comparisons to placebo were performed on the observed number and severity of hot flushes with baseline as a covariant. No procedure for carrying forward missing data was implemented.
5) Irregularities in endometrial biopsies consensus procedure and diagnosis; one subject diagnoses by majority opinion as malignancy reported as hyperplasia (0.45 CEE/1.5 mg MPA), and one subject with a discordant diagnosis was not referred to third pathologist (diagnosis of endometrial malignancy and complex hyperplasia with atypia [0.3 mg CEE]) and was given the diagnosis determined by a referral gynecologic oncologist.
6) Adverse events of note include 8 reports of breast cancer (1 post-study), 7 cases of vascular thromboses (CVA, MI, DVT, pulmonary embolism) including one case with a transient ischemia attack (TIA is not reported in current labeling, a 15-day IND Safety Report was sent).

Attachment: 45-Day Filing Meeting Checklist
Cc: NDA 20-527 Division File
HFD-580/DMoore/SSlaughter/TvanderVlugt

NDA: 20-527/S-017

45 Day Filing Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) Is the clinical section of the NDA clearly organized?	X		
2) Is the clinical section of the NDA adequately indexed and paginated?	X		
3) Is the clinical section of the NDA legible?	X		
4) Is there an adequate rationale for selection of dose and dosing schedule?	X		
5) Are the requisite number of adequate and well controlled studies submitted in the application?	X		
6) Are the pivotal efficacy studies of appropriate design and duration to assess approvability of this product for its proposed indication?	X		Study design for protection of the endometrium and the treatment of VVA was appropriate. However, for the treatment of vasomotor symptoms a subgroup analysis had to be performed due to the absence of appropriate inclusion criteria for the baseline number of moderate-to-severe hot flushes.
7) Are electronic data sets (with adequate documentation for their use) provided for pivotal efficacy studies?			
8) Has the applicant submitted line listings in a format to allow review of individual patient data?	X		
9) Has the applicant submitted a rationale for assuming the applicability of foreign trial results to the U.S. population?	NA		
10) Has the applicant submitted all required case report forms (i.e., deaths, drop-outs due to ADEs and any other CRFs previously requested by the Division?	X		
11) If appropriate, have stratified analyses of primary safety and efficacy parameters been conducted for age, gender and race?	NA		
12) Has the applicant presented the safety data in a manner previously agreed to by the Division?	X		
13) If approved in other countries, have a summary and assessment of foreign post-marketing experience been provided?	NA		
14) Has draft labeling been submitted?	X		

15) Have all special studies/data requested by the Division during pre-submission discussions with the sponsor been submitted?	X		
16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	X		
17) Reasons for refusal to file:			

/S/ 8/1/00
Reviewing Medical Officer/Date

/S/ 8/1/00
Medical Team Leader/Date

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 8/1/00 8:46:45 AM
From: Krishan Raheja RAHEJA)
Subject: NDA 20-527/S-017 filing meeting

Diane,

Since both CE and MPA doases proposed are lower than already approved, Pharmacology has no objection to filing.

Krishan

APPEARS THIS WAY
ON ORIGINAL