Minutes of Teleconference

Date: April 20, 2000 **Time**: 9:30 - 9:50 AM **Location:** Parklawn; Ms. Moore's Office

NDA: 20-527 **Drug Name**: Prempro™ (conjugated estrogens/medroxyprogesterone acetate) tablets

Type of Meeting: Guidance (statistical)

External Participant: Wyeth-Ayerst Research

Meeting Chair: Dr. Lisa Kammerman **External Participant Lead**: Ms. Mary Beth Thompson

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
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 Constituents:
Paul Hansen – IT Engineer, Global Clinical Programming
Michelle Lucas – Senior Statistician, Global Clinical Biostatistics
Mary Beth Thompson – Standards Manager, Global Regulatory Information & Documentation
Joseph Sonk, Ph.D. - Senior Director, Therapeutic Area Head Women's Health, Worldwide Regulatory Affairs
JoAnne M. Bissinger – Manager, Worldwide Regulatory Affairs

Meeting Objective:
To discuss proposed submission of SAS data sets for an efficacy supplement to NDA 20-527 (see telefacsimile dated April 18, 2000).

Background: Wyeth-Ayerst received an electronic mail message from Randy Levin regarding their April 18, 2000, proposal (see attached April 20, 2000 telefacsimile).

Discussion Points:

- Proposal 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. The purpose of this is to reduce the number of files by a factor of three.
  - Randy Levin agreed with this proposal
  - additionally, the sponsor proposed that a missing value would be assigned to patients who did not take study medication for "duration of study"
- Proposal 2: 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 approximately equal sized files. Note that some investigators have so much bleeding and symptom data, that their data will exceed 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).

- Randy Levin disagreed with this proposal and suggested an alternative; he suggested the laboratory values be separated into smaller groups (e.g., electrolytes, LFTs, etc) before dividing them by investigator and separating bleeding times and vasomotor symptoms into separate files
- the sponsor feels that the large number of records in this study will not divide well into the suggested categories; the sponsor prefers to divide the files by investigator and sequential patient numbers

Decisions reached:

- FDA response to Proposal 1:
  - the Division finds Proposal 1 acceptable
- FDA response to Proposal 2:
  - the files can be divided by investigators and sequential patient numbers, as proposed
  - all demographic variables (gender, age, ethnic group, body mass index, years since menopause, etc.) will be included in a demographic data set in Item 11 of the NDA; only the demographics for gender, age, and ethnic group will be included in other files
- Additional Comments
  - in addition to the above files, an analysis data set should be submitted for the relief of moderate-to-severe vasomotor symptoms indication

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• send copy of Telecon minutes	Ms. Moore	1 month

/S/ 4/27/00
Signature, minutes preparer

/S/
Concurrence, Chair 5/17/00

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/4.20.00/N20527TC42000

Concurrence:
LKammerman 4.21.00
cc:
NDA Arch:
HFD-580/Div File
HFD-580/SAllen/MMann/SSlaughter/Tvander Vlugt/TRumble/LKammerman

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 ORIGINAL

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

Telefax Number: (610) 964-5973

DATE: April 20, 2000

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

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

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

NO. of PAGES: *3 (including cover page)*

SUBJECT: *April 20, 2000 Teleconference - Efficacy Supplement for NDA 20-527 (Conjugated Estrogens/ Medroxyprogesterone Acetate)*

Diane,
As requested at today's teleconference, I am providing you with a copy of the e-mail we received from Randy Levin of the FDA regarding our proposals for the electronic submission of Item 11 (Attached).

In addition, I am providing you with the names and titles of Wyeth-Ayerst personnel who participated in today's teleconference.

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*

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

JoAnne M. Bissinger

From: "Randy Levin 301-594-5514 FAX 301-594-2859" <LEVINR@cder.fda.gov>
To: "Mary Beth Thompson" <ThompsM4@war.wyeth.com>, "es...
Date: Mon, Apr 17, 2000 8:30 PM
Subject: Re: Questions about SAS XPT / Item 11 submissions

See comments below:

>Randy and Ken,
>
>We are preparing an electronic submission and I've been asked to run this by your to see if this would be compliant with your standards. Here is a quick summary of some of the proposals discussed in a meeting this afternoon concerning the Item 11 electronic datasets for the HOPE submission.
>
>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.

---This should be ok.

>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).

>
>Do you think we are going down the right track with these assumptions? Or would you recommend something else? We are in the process of setting up a teleconference with the reviewing division (including stats), but I'd still like to get your input.

----->For the lab data, I would separate the labs into smaller groups (e.g., electolytes, LFTs, etc) before dividing them by investigator. I

would separate the bleeding times and vasomotor symptoms into separate files. If these events are for efficacy data, you may be able to provide files larger than 25 MB if the statisticians are going to use them in directly in SAS.

>
>Thanks.
>
>MaryBeth Thompson
>Standards Manager
>Global Regulatory Information & Documentation
>
>610-902-5245
>8 370-5245
>
>

APPEARS THIS WAY
ON ORIGINAL

Minutes of Teleconference

Date: April 22, 1999 **Time**: 3:30 - 3:50 PM **Location:** Parklawn; Room 17B-43

[redacted] **Drug Name**: Premarin (conjugated estrogens) and medroxy-progesterone acetate (MPA)

Type of Meeting: Chemistry Guidance

External Participant: Wyeth-Ayerst Research

Meeting Chair: Dr. Lisa Rarick **External Participant Lead**: Mr. Doug Bits

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 Constituents:
Douglas W. Bitz - Director, U.S. Drug Regulatory Affairs, Wyeth-Ayerst, Radnor, PA
Joseph Sobecki – U.S. Regulatory Affairs, Wyeth-Ayerst, Radnor, PA
John Mesunas – Analytical Research and Development, Stability, Pearl River, NY
Alan Kutz, Ph.D. - Analytical Research and Development, Pearl River, NY
Arwinder Nagi, Ph.D. - Formulations, Pearl River, NY
Debra Parker – Regulatory Information, Pharmaceutical Sciences, Pearl River, NY
Roger French, Ph.D. - Biometrics, Pearl River, NY

Meeting Objective: To discuss the stability protocol for the lower dose of Premarin MPA.

Background: The current drug release specifications for Premarin + MPA adhere to the drug release specifications with the 8-hour profile for conjugated estrogens in Supplement 8, USP 23, from May 15, 1998.

Discussion Points:
- although Prempro/Premphase does not have the same dissolution specifications as in Supplement 8 of the USP, it is consistent with the Premarin data collection in the 8-hour dissolution method
- currently the sponsor is collecting dissolution data by both the previous and the revised dissolution methods testing schemes
- all methods being used for stability for this proposed protocol (HOPE study) are the same as those being currently used for NDA 20-527 (Prempro/Premphase)
- the sponsor is applying two different dissolution methods for MPA; the additional testing method is being conducted for informational purposes only

Meeting Minutes - April 22, 1999

Decisions reached:

- the protocol is acceptable

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• send meeting minutes	Ms. Moore	May 22, 1999

/S/ 5/5/99
Signature, minutes preparer

/S/ 5/5/99
Concurrence, Chair

drafted: dm/April 26, 1999

cc:
NDA Arch:
HFD-102/JBilstad
HFD-102/FHoun
HFD-580/LRarick/MMann/DLin/MRhee
HFD-580/DMoore

Concurrence:
TRumble 04.28.99/DLin 05.03.99

APPEARS THIS WAY
ON ORIGINAL

End of Phase 2 and Pre-NDA meetings

No End of Phase 2 or Pre-NDA meetings were held for this efficacy supplement.

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.

Advisory Committee Meeting Minutes

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

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.

Federal Register Notices

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

Confirmation Report – Memory Send

Page : 001
Date & Time: Mar-12-03 06:20pm
Line 1 : 301-827-4267
Line 2 :
Machine ID : FDA/CDER/OND/ODE3/DRUDP

Job number : 357

Date : Mar-12 06:09pm

To : ☎914848659214

Number of pages : 037

Start time : Mar-12 06:09pm

End time : Mar-12 06:20pm

Pages sent : 037

Status : OK

Job number : 357 *** SEND SUCCESSFUL ***

5600 Fishers Lane, Rockville, Maryland 20857

Food & Drug Administration
Division of Urologic and
Reproductive Drug Products

Fax

To: Jennifer Norman From: Kasandra Steward

Fax: 484-825-9214 Pages:

Phone: 484-825-3749 Date: March 12, 2003

Re: NDA 20-527/017 CC:

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

• Comments:

5600 Fishers Lane, Rockville, Maryland 20857

Food & Drug Administration
Division of Urologic and Reproductive Drug Products

Fax

To:	Jennifer Norman	**From:**	Kassandra Sherrod
Fax:	484-865-9214	**Pages:**	
Phone:	484-865-3749	**Date:**	March 12, 2003
Re:	NDA 20-527/017	**CC:**	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 20-527	Efficacy Supplement Type SE- 2	Supplement Number 017
Drug: Prempro™/Premphase (0.45mg CE/1.5mg MPA)		Applicant: Wyeth-Ayerst Laboratories
RPM: Kassandra Sherrod	HFD- 580	Phone #
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(✓) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	4/15/01, 6/15/01, 3/12/03
❖ Special programs (indicate all that apply)	(✓) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(✓) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (✓) No
• This application is on the AIP	( ) Yes (✓) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(✓) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(✓) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified N/A
Exclusivity Summary (approvals only)	✓
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	

General Information	
Actions	
• Proposed action	(✓) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE 4/13/01
• Status of advertising (approvals only)	(✓) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(✓) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (✓) Press Release (✓) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	✓
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	✓
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	✓
• Reviews	
Post-marketing commitments	
• Agency request for post-marketing commitments	✓
• Documentation of discussions and/or agreements relating to post-marketing commitments	✓
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	✓
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	none held
• Pre-NDA meeting (indicate date)	none held
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	Status meetings
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Clinical and Statistical Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	3/12/03
❖ Clinical review(s) *(indicate date for each review)*	3/12/03
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Statistical review(s) *(indicate date for each review)*	
❖ Biopharmaceutical review(s) *(indicate date for each review)*	
Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	

Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	3/10/03, 4/13/01
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	N/A
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: (✓) Acceptable 2/3/03 ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested N/A ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 20-527 / SE 2 - 017

Drug Tradename conjugated estrogens/medroxyprogesterone tablets 0.3/1.5 mg and 0.45/1.5 mg

Applicant Wyeth-Ayerst Laboratories

RPM Diane Moore

Phone 301 827-4260

X505(b)(1)
☐505(b)(2) Reference listed drug

☐Fast Track ☐Rolling Review Review priority: X S ☐P

Pivotal IND(s) [redacted]

Application classifications:
Chem Class 3011000
Other (e.g., orphan, OTC)

PDUFA Goal Dates:
Primary April 15, 2001
Secondary June 15, 2001

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: X User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption
- Action Letter ..... ☐AP X AE ☐NA
- Labeling & Labels
  - FDA revised labeling and reviews X
  - Original proposed labeling (package insert, patient package insert) 6/15/00
  - Other labeling in class (most recent 3) or class labeling ..... Class labeling
  - Has DDMAC reviewed the labeling? ..... XYes (include review) ☐ No
  - Immediate container and carton labels 6/15/00
  - Nomenclature review ..... 3 reviews
- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application Xis X is not on the AIP.
  - Exception for review (Center Director's memo) ..... N/A
  - OC Clearance for approval ..... N/A

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) — X Materials requested in AP letter

- Post-marketing Commitments — N/A
  - Agency request for Phase 4 Commitments X
  - Copy of Applicant's commitments X

- Was Press Office notified of action (for approval action only)? ..... ☐ Yes X No
  - Copy of Press Release or Talk Paper ..... N/A

- Patent
  - Information [505(b)(1)] X
  - Patent Certification [505(b)(2)] X
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)] ..... N/A

- Exclusivity Summary X

- Debarment Statement X

- Financial Disclosure
  - No disclosable information ..... N/A
  - Disclosable information – indicate where review is located ..... June 15 and November 22, 2000 submissions

- Correspondence/Memoranda/Faxes X

- Minutes of Meetings X
  - Date of EOP2 Meeting No EOP2 meeting held
  - Date of pre NDA Meeting No pre NDA meeting held for this supplement
  - Date of pre-AP Safety Conference N/A

- Advisory Committee Meeting ..... N/A
  - Date of Meeting ..... N/A
  - Questions considered by the committee ..... N/A
  - Minutes or 48-hour alert or pertinent section of transcript ..... N/A

- Federal Register Notices, DESI documents ..... N/A

CLINICAL INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) X

- Clinical review(s) and memoranda X

- Safety Update review(s) ..... See M.O. review

Continued ⇨

- Pediatric Information
  X Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... X
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted X Not Applicable

- Statistical review(s) and memoranda X

- Biopharmaceutical review(s) and memoranda..... X

- Abuse Liability review(s) ..... N/A
  Recommendation for scheduling ..... N/A

- Microbiology (efficacy) review(s) and memoranda ..... N/A

- DSI Audits ..... N/A
  ☐Clinical studies ☐ bioequivalence studies ..... N /A

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- CMC review(s) and memoranda X

- Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A

- DMF review(s) X

- Environmental Assessment review/FONSI/Categorical exemption ..... N/A

- Micro (validation of sterilization) review(s) and memoranda ..... N/A

- Facilities Inspection (include EES report)
  Date completed April 12, 2001 ..... ☐ Acceptable X Not Acceptable

- Methods Validation ..... ☐ Completed ☐ Not Completed
  CE completed; MPA not completed

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Pharm/Tox review(s) and memoranda X

- Memo from DSI regarding GLP inspection (if any) ..... N/A

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

APPEARS THIS WAY
ON ORIGINAL

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

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Wyeth-Ayerst Laboratories

P.O. Box 8299
Philadelphia, PA 19101-8299

2. TELEPHONE NUMBER *(Include Area Code)*

(610) 902-3740

3. PRODUCT NAME

Conjugated Estrogens and Medroxyprogesterone Acetate

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO
(APPLICATION NO. CONTAINING THE DATA)

5. USER FEE I.D. NUMBER

3947

6. LICENSE NUMBER / NDA NUMBER

NDA No. 20-527

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetics Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

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Joseph S. Sonk, PhD	Senior Director, Global Therapeutic Area Head, Women's Healthcare Worldwide Regulatory Affairs	May 23, 000

FORM FDA 3397 (5/98)

FACSIMILE TRANSMISSION

Wyeth-Ayerst Laboratories
St. Davids Center
170 Radnor-Chester Road
St. Davids, PA 19087
USA

FAX #'S: *(610) 964-5972*
(610) 964-5969

Date: April 11, 2001

To: Dr. Susan Allen

From: Joseph S. Sonk

Department: Worldwide Regulatory Affairs

Number of Pages (*including cover sheet):* 44

Please call me at (610) 902-3740 with any questions.

WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

JAMES E. MONK, PhD
Assistant Vice President
Worldwide Regulatory Affairs

April 11, 2001

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

VIA FAX

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

Dear Dr. Allen:

Reference is made to NDA No. 20-527/S-017 for PREMPRO (conjugated estrogens/ medroxyprogesterone acetate tablets), PREMPHASE (conjugated estrogens/ medroxyprogesterone acetate tablets) submitted to DRUDP on June 15, 2000. Reference is also made to FDA's fax of April 4, 2001 that contained the Division's draft labeling for this supplement as well as comments in regard to Wyeth-Ayerst's proposal for a new proprietary name for the lower strength tablets.

Attached is Wyeth-Ayerst's response to the Division's April 4th fax. The major points in this draft labeling are:

- In the section titled "Information regarding effects on Vasomotor Symptoms", a table named "A Summary tabulation of the number of Hot Flushes" was added as requested. We have also retained the previously submitted chart which captures the information in the table because it demonstrates that the effects of the drug begin as early as 2 weeks and we believe this information is important to the prescriber.

- In the section titled "Information Regarding Effects On Vulvar and Vaginal Atrophy", a table named "Vaginal Maturation Index" has been added to highlight the results seen at Cycles 6 and 13.

- In the section titled "Information Regarding Control of Bleeding", we have retained the graphic displays for both the Efficacy Evaluable and Intent to Treat populations for both the 0.625/2.5mg and 0.45/1.5mg strengths evaluated in the HOPE study. We understand the Division's recommendations about this section but believe our suggestion is also meaningful because the practicing physician needs to understand the results achieved in both populations in order to appropriately prescribe the drug. These data displays have been an important part of the approved Package Insert since the initial launch of Prempro and we believe they are a key part of the labeling.

- Table 13 "Percent of Patients Reporting ≥ 5% Treatment Emergent Adverse Events" has been updated to reflect the information submitted to the Division on March 29, 2001.

- The Patient Package Insert has been revised extensively to comply with the Division's letter to Wyeth-Ayerst dated February 21, 2001.

Please note that this draft labeling refers to the Prempro tradename for all strengths and we acknowledge FDA's recommendation that this should be the tradename for all strengths of CE/MPA. We would like to further discuss this issue, from the prescriber's perspective, at the earliest possible convenience.

If you have any questions regarding this submission, please contact me at (610) 902-3740.

Sincerely,

WYETH-AYERST LABORATORIES

Joseph S. Sonk, Ph.D.
Assistant Vice President, Worldwide Regulatory Affairs
Global Therapeutic Area Head, Women's Health Care

Desk Copy – Diane Moore

JSS.bch/0012

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.

Abuse Liability review

There is no abuse liability potential for this approved drug product. No abuse liability review was performed for this supplemental application.

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.

Microbiology Review

No microbiology review is required for oral Tablets.

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.

DSI memo regarding GLP inspection

No GLP inspection was required for this efficacy supplemental application because all dosage strengths of this product have previously been approved.

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

.TE RECEIVED:	DUE DATE:	OPDRA CONSULT #:
February 20, 2001	March 5, 2001	01-0045

TO: Susan Allen, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Diane Moore, Project Manager
HFD-580

PRODUCT NAME:	**MANUFACTURER**: Wyeth-Ayerst Laboratories
(Conjugated Estrogens and Medroxyprogesterone Acetate Tablets) 0.45 mg/1.5 mg and 0.3 mg/1.5 mg **NDA #: 20-527/SL-017**	

SAFETY EVALUATOR: Carol Holquist, R.Ph.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), OPDRA conducted a review of the sponsor's February 6, 2001 submission containing survey data in support of reconsideration of the acceptability of a new proprietary name for a low dose version of the currently marketed "Prempro". In addition, OPDRA reviewed the proposed labels and labeling for the new product strengths.

OPDRA RECOMMENDATION: The applicant has failed to provide persuasive evidence to minimize OPDRA's concern with regard to the addition of a new proprietary name for the lower strengths of this combination product. OPDRA recommends the continued use of the previously approved proprietary name PREMPRO for the new strengths with the addition of the strength modifiers as outlined in OPDRA consult 00-0321.

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Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: **February 23, 2001**

NDA NUMBER: **20-527/SL-017**

NAME OF DRUG: [redacted] **(Conjugated Estrogens and Medroxyprogesterone Acetate Tablets) 0.45 mg/1.5 mg and 0.3 mg/1.5 mg**

NDA HOLDER: **Wyeth-Ayerst Laboratories**

I. INTRODUCTION

On June 15, 2000, the sponsor submitted a supplement (S-017) to NDA 20-527 for the addition of two new strengths of the combination estrogen/progestin tablet currently marketed as PREMPRO. Each PREMPRO tablet contains 0.625 mg conjugated estrogen (CE) and either 5 mg or 2.5 mg of medroxyprogesterone acetate (MPA). The *new* lower strength tablet will contain either 0.45 mg or 0.3 mg of conjugated estrogens and 1.5 mg of medroxyprogesterone acetate.

On August 14, 2000, the Division requested OPDRA review the sponsor's proposal for a new proprietary name for the additional product strengths. The sponsor stated that there had been some confusion in the marketplace with the currently marketed products PREMPRO/PREMPHASE and the new tradename would resolve this conflict. However, OPDRA conducted a post-marketing review on medication errors associated with PREMPRO and PREMPHASE on March 17, 2000 (OPDRA consult 00-0076), in which we concluded that the medication errors were attributed to similar labeling rather than proprietary name confusion. Although some reports mentioned the sound-alike/look-alike potential of these proprietary names, the majority of actual medication errors involved complaints of similar packaging between PREMPRO and PREMPHASE and confusion surrounding the use of an identical established name for both drug products. Based on this previous consult, OPDRA concluded that the addition of a new name would not resolve the conflict regarding confusion between these two products.

The Division notified the sponsor of OPDRA's decision. On November 10, 2000, the sponsor submitted further rationale for the proposal of a new tradename. OPDRA concluded that the sponsor did not provide persuasive evidence to minimize the concern with regard to the addition of a new proprietary name for the lower strengths of this combination product. OPDRA recommended the continued use of the previously approved proprietary name PREMPRO for the new strengths with the addition of the strength modifiers as outlined below.

PREMPRO **0.625/2.5**

PREMPRO **0.625/5**

PREMPRO **0.45/1.5**

PREMPRO **0.3/1.5**

We also recommended differentiating the product strengths with the use of contrasting color, boxing or some other means.

On February 6, 2001 the sponsor submitted the results of three surveys which were conducted to further support their proposal of the use of a new tradename for the low dose product. This consult is written in response to the Division's request to review and comment on this additional information provided to support the sponsor's proposal. In addition, we were requested to review the accompanying product labels and labeling.

II. RISK ASSESSMENT

A. The sponsor proposes the proprietary name, ——— 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 contain a different estrogen and progestin dosage than the marketed PREMPRO products. Wyeth Ayerst conducted three separate surveys to further support the use of this additional proprietary name.

1. Physician Survey

This survey was conducted from January 15, 2001 to January 17, 2001. One hundred and thirty six (136) OB/GYN physicians responded to the survey via fax. Respondents were asked a series of three questions:

Question 1: Do you believe that branding this new product, as Prempro would be confusion to both you and the pharmacist in ensuring that the patient gets the appropriate dose?

The response rate was fairly equal among physicians surveyed. Seventy-three physicians thought the use of the proprietary name Prempro would cause confusion to themselves as well as pharmacists. However, sixty-three did not believe that branding the new strength, as Prempro would be confusing. It is unclear from the information provided if the selected physicians currently prescribe Prempro on a routine basis.

Question 2: If this new lower dose combination HRT product were to have a name other than Prempro, would prescribing the product be less confusing?

Eighty-four physicians thought the use of another proprietary name would be less confusing.

Question 3: If the product were given a name other than Prempro, do you believe it would also be less confusing for the pharmacist and therefore you would field fewer pharmacist calls to determine the appropriate dose?

Ninety-four physicians believed that a new name would be less confusing and would require fewer calls from the pharmacist for clarification.

In addition, a few physicians provided some product name recommendations such as [redacted]. It is important to note that although practitioners stated a new proprietary name would be less confusing, the names that were suggested contained the *Prempro* name.

2. Pharmacist Survey

One hundred and eleven retail pharmacies (73 independents and 38 chain) responded to this survey which was conducted during a one-week period in January 2001. Participating pharmacies were each faxed a brief survey asking their opinions on whether a new low dose combination estrogen/progestin should be identified with a new brand name or be identified as Prempro 1.5/0.45 mg. Each participant was given the following statement as an introduction to the research questions: Wyeth-Ayerst, the manufacturer of Premarin and Prempro, is planning to introduce a new low dose HRT Conjugated Estrogen/MPA combination product. This new dose would contain:

0.45 mg of conjugated estrogen
and
1.5 mg of MPA

This dosing is lower than the currently available Prempro (0.625 mg of conjugated estrogen/ 2.5 mg of MPA).

Participants were requested to answer the following series of questions:

Question 1: With respect to filling prescriptions for this new dosage, would you prefer, (please check one)
_____the new dosage be given its own brand name
OR
_____the new dosage be identified as "Prempro.45/1.5"

Sixty-nine percent (69%) of pharmacies surveyed responded "the new dosage be given its own brand name". The majority of pharmacies surveyed were retail pharmacies dispensing greater than 1000 prescriptions per week. We recognize that in this type of setting with such a demanding workload, pharmacists would have ***limited time*** to call prescribers to clarify prescriptions that did not include the product strength on the prescription. However, dosage clarifications can also provide the opportunity of a positive intervention, in that it allows the pharmacist another chance to verify the correct drug with the prescriber prior to dispensing.

Question 2: Do you believe that branding this product as Prempro .45/1.5 would cause confusion among pharmacists and physicians in ensuring that the patient gets the appropriate dose?

___Yes
___No

Seventy-three percent (73%) responded yes. The majority of respondents were retail pharmacies who dispensed a high volume of prescriptions (500 –1000) per week. In this busy setting it is difficult to ensure the accuracy of any medication dispensed.

Question 3: Which would provide **greater** confusion for pharmacists in dispensing prescriptions for this new product?

___New brand name
___Prempro .45/1.5

Seventy-two percent (72%) responded Prempro .45/1.5. The majority of respondents were pharmacies that dispensed a high volume of prescriptions (>1000) per week.

It is interesting that 66% of the pharmacies surveyed were independents. This type of pharmacy is not representative of where the majority of prescriptions are filled within the United States. National chain pharmacies accounted for only 24% of the population of pharmacies surveyed.

3. Qualitative Research Project

This research project was conducted in two phases, each phase included twenty physicians from different geographic locations during November 2000 and January 2001. The physicians were divided between OB/GYNs and Primary Care Physicians (PCPs) in office based practices that were high prescribers for HRT. A summary of the findings was the only item provided for review. The sponsor did not provide detailed information on how the physicians were interviewed or what questions that were asked.

The majority of physicians preferred retaining the Prempro name. They believed this name would be less confusing and easier to remember. Retention of the product name, Prempro, signaled that the product contained the same components with a different dosage. Those that did prefer the new name, [redacted], cited that fact that they currently received phone calls from pharmacies requesting clarification on the dosages.

Although dosage clarifications can be considered an inconvenience, OPDRA believes they can also provide the opportunity of a positive intervention, in that it allows the pharmacist another chance to verify the correct drug with the prescriber prior to dispensing.

It is important to note that although physicians did not like having to include the specific dosages most were in the habit of doing so already. They stated it was easier to learn the dosages that to remember a new name.

We can conclude from the surveys that most physicians preferred the retention of the proprietary name Prempro or some variation of this name for the same reasons we stated in our previous consult (launching the new low dose CE/MPA products under a new tradename is misleading to health care professionals, in that it infers a different product, launching under the existing PREMPRO tradename, would require physicians to designate the CE dosage and

the MPA dosage when prescribing the desired dose, and that this would eliminate the past confusion demonstrated when these descriptors were missing from the ordering process).

In addition, pursuant to a December 1, 2000, CDER policy meeting with the Center Director, Janet Woodcock, M.D. and senior management, OPDRA will no longer recommend approval of different proprietary names by the same applicant or manufacturer for products that are essentially identical unless there is a public health risk or stigma associated with the use of the drug product. The Agency is concerned with the proliferation of proprietary names for the following reasons:

Safety Concerns:

- *Overdose:* Practitioners may become confused and not understand that the two products (with 2 different trade names) are identical. This may increase the risk of a patient being prescribed the same drug product by different physicians, resulting in an overdose.
- *Medication errors:* The creation of a new proprietary name for a new strength of an essentially identical drug product adds unnecessarily to the growing number of proprietary names in the United States. This proliferation of numerous proprietary names may increase the likelihood of occurrence of medication errors resulting in patient injury due to sound-alike and/or look-alike confusion between products.
- *Confusion/Misleading*: Trivialization of the adverse events and risks associated with the use of different proprietary names for the same active moiety. Patients may be falsely assured that the medication does not carry significant risks because the FDA has allowed its use for a relatively benign condition.

Other Concerns:

- *False Inference*: The separate proprietary name infers that there is a unique efficacy that is deserving of a separate name, when in fact this is not true.
- *Management of ADE:* The increasing complexity to manage (regulatory) reports of adverse drug events associated with one active ingredient with 2 or more proprietary names.
- *Labeling Implications and Agency Burden:* The approval of a NDA supplement for an essentially identical drug product will have a negative impact on Agency and Industry resources. There are several consequences with the labeling and packaging of two identical drug products with two different proprietary names. A separate ANDA would be required for each referenced drug, thus increasing the time expenditure for OGD chemistry and bioequivalency reviews as well. Two different proprietary names within one NDA would require two sets of labeling. Once an NDA patent expires, a generic applicant would have to decide whether or not to file a new ANDA in order to market the "same product" for another strength.
- *Pharmacy Burden:* The proliferation of numerous proprietary names for the same active ingredient places an inventory and storage burden on pharmacies and pharmacists.

We believe there are no public health risks or stigmas associated with the use of one proprietary name for this drug product. Therefore, the safe use of this product is best managed under one proprietary name.

B. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

CONTAINER LABEL and CARTON LABELING

We recommend differentiating the product strength with the use of boxing contrasting colors or some other means. It may be advantageous to color code the labels and labeling in a similar manner as Premarin where the color used to differentiate the labels and labeling match the color of the tablet.

IV. COMMENTS TO BE PROVIDED TO SPONSOR

We recommend differentiating the product strengths with the use of boxing contrasting colors or some other means. It may be advantageous to color code the labels and labeling in a similar manner as Premarin where the color used to differentiate the labels and labeling match the color of the tablet.

V. RECOMMENDATIONS

The applicant has failed to provide persuasive evidence to minimize OPDRA's concern with regard to the addition of a new proprietary name for the lower strengths of this combination product. OPDRA recommends the continued use of the previously approved proprietary name PREMPRO for the new strengths with the addition of the strength modifiers as previously suggested.

OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact the project manager, Sammie Beam, R.Ph., at 301-827-3231.

Carol Holquist, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

/s/

Carol Holquist
3/5/01 12:16:27 PM
PHARMACIST

Jerry Phillips
3/5/01 12:24:15 PM
DIRECTOR

Martin Himmel
3/8/01 12:20:23 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED:	DUE DATE:	OPDRA CONSULT #:
February 20, 2001	March 5, 2001	00-0076-2

TO: Susan Allen, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Diane Moore, Project Manager
HFD-580

PRODUCT NAME:	MANUFACTURER:
PREMPRO™ (Conjugated Estrogens and Medroxyprogesterone Acetate Tablets) 0.625 mg/2.5 mg and 0.625 mg/5 mg **PREMPHASE®** (Conjugated Estrogens Tablets 0.625 mg and Conjugated Estrogens and Medroxyprogesterone Acetate Tablets 0.625 mg/5 mg) **NDA #: 20-527/S-018**	Wyeth-Ayerst Laboratories, Inc.

SAFETY EVALUATOR: Carol Holquist, R.Ph.

SUMMARY: This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products, to review and comment on the revised container label, carton and insert labeling of Prempro and Premphase in response to an OPDRA post-marketing consult that described 15 cases of medication error due to similar labeling.

OPDRA RECOMMENDATION: After review of the information submitted by the sponsor, OPDRA has provided further labeling revisions (see review).

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Office of Post-Marketing Drug Risk Assessment
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Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

5 pages

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED:	DUE DATE:	OPDRA CONSULT #:
November 20, 2000	January 16, 2001	00-0321

TO: Susan Allen, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Diane Moore, Project Manager
HFD-580

PRODUCT NAME: [redacted] (Conjugated Estrogens and Medroxyprogesterone Acetate Tablets) NDA #: 20-527/S-017	MANUFACTURER: Wyeth-Ayerst Laboratories, Inc.

SAFETY EVALUATOR: Carol Holquist, R.Ph.

SUMMARY: This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products, to review and comment on the sponsor's request for reconsideration of the acceptability of a new proprietary name for a low dose version of the currently marketed "Prempro".

OPDRA RECOMMENDATION: After review of the information submitted by the sponsor, OPDRA does not recommend the use of a new proprietary name for this drug product.

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Office of Post-Marketing Drug Risk Assessment
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Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: **December 20, 2000**

NDA NUMBER: **20-527/S-017**

NAME OF DRUG: [redacted]
(Conjugated Estrogens and Medroxyprogesterone Acetate Tablets)

NDA HOLDER: **Wyeth-Ayerst Laboratories**

I. INTRODUCTION

On June 15, 2000, the sponsor submitted a supplement (S-017) to NDA 20-527 for the addition of two new strengths of the combination estrogen/progestin tablet currently marketed as PREMPRO. Each PREMPRO tablet contains 0.625 mg conjugated estrogen (CE) and either 5 mg or 2.5 mg of medroxyprogesterone acetate (MPA). The *new* lower strength tablet will contain either 0.45 mg or 0.3 mg of conjugated estrogens and 1.5 mg of medroxyprogesterone acetate.

On August 14, 2000, the Division requested OPDRA review the sponsor's proposal for a new proprietary name for the additional product strengths. The sponsor stated that there had been some confusion in the marketplace with the currently marketed products PREMPRO/PREMPHASE and the new tradename would resolve this conflict. However, OPDRA conducted a post-marketing review on medication errors associated with PREMPRO and PREMPHASE on March 17, 2000 (OPDRA consult 00-0076), in which we concluded that the medication errors were attributed to similar labeling rather than proprietary name confusion. Although some reports mentioned the sound-alike/look-alike potential of these proprietary names, the majority of actual medication errors involved complaints of similar packaging between PREMPRO and PREMPHASE and confusion surrounding the use of an identical established name for both drug products. Based on this previous consult, OPDRA concluded that the addition of a new name would not resolve the conflict regarding confusion between these two products.

The Division notified the sponsor of OPDRA's decision. On November 10, 2000, the sponsor submitted further rationale for the proposal of a new tradename. This consult is written in response to the Division's request to review and comment on this additional information provided to support the sponsor's proposal.

PRODUCT INFORMATION

Prempro therapy consists of a single tablet containing 0.625 mg of the conjugated estrogens and 2.5 mg or 5 mg of medroxyprogesterone acetate for oral administration. Prempro is indicated in women with an intact uterus for the treatment of moderate to severe vasomotor symptoms associated with the menopause, [redacted] vulvar and vaginal atrophy, and the prevention of osteoporosis.

II. RISK ASSESSMENT

The sponsor proposes the proprietary name [redacted] 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 following represents their rational and OPDRA's response to this rational.

A. *SPONSOR COMMENT*

The initial NDA for PREMPRO/PREMPHASE single combined tablets (NDA 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.

OPDRA RESPONSE

Dosage clarifications between physicians and pharmacists are not uncommon with any drug product especially when multiple strengths are involved. Although dosage clarifications can be considered an inconvenience, they can also provide the opportunity of a positive intervention, in that it allows the pharmacist another chance to verify the correct drug with the prescriber prior to dispensing.

We believe that the addition of the new lower strengths would require physicians to practice better prescribing habits with this drug product. Physicians would have to include the dosage of each ingredient on the prescription or they will be overwhelmed with telephone calls from other health care practitioners regarding strength clarification.

B. *SPONSOR COMMENT*

We believe it is important from a prescribing prespective 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. 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 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] 0.45 mg or [redacted] 0.3 mg.

OPDRA RESPONSE

The sponsor states that "it would be 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". This statement contradicts the sponsors previous statement 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". Thus, demonstrating there is no clearly established prescribing practice for PREMPRO.

OPDRA believes launching the new low dose CE/MPA products under a new tradename is misleading to health care professionals, in that it infers a different product. Launching under the existing PREMPRO tradename, would require physicians to designate the CE dosage and the MPA dosage when prescribing the desired dose. This would eliminate the past confusion demonstrated when these descriptors were missing from the ordering process. OPDRA recommends including the labeled amount of each active ingredient in conjunction with the proprietary name as follows:

PREMPRO **0.625/2.5**

PREMPRO **0.625/5**

PREMPRO **0.45/1.5**

PREMPRO **0.3/1.5**

We also recommend differentiating the product strengths with the use of contrasting color, boxing or some other means.

C. *SPONSOR COMMENT*

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. The 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.

OPDRA RESPONSE

We recognize that separate tradenames for products with the same active ingredients have been approved by the Agency in the past. However, new policies and procedures involving proprietary name reviews have been implemented since approval of the above referenced products. The Agency routinely discourages the addition of a separate tradename for products containing the same active ingredients for the following reasons:

⇒The creation of another proprietary name for a new strength or indication adds unnecessarily to the growing number of tradenames in the United States, thus creating additional safety concerns.

⇒OPDRA believes that having 2 tradenames by the same manufacturer, for the same bioequivalent drug product is misleading to health care professionals, in that it infers a different product.

Orudis and Oruvail contain the same active ingredient "Ketoprofen". However, Orudis is an immediate release capsule and Oruvail is an extended-release capsule, each requiring different dosages and dosing intervals (three times daily and once daily). Under current guidelines the use of a modifier would be the acceptable alternative to a new tradename.

OPDRA believes the use of different proprietary names with regard to oral contraceptives is important. There are numerous combination oral contraceptive products on the market with varying cyclic phase administration making it impossible for health care providers to keep track of the amount of the active ingredient contained in each of the different formulations. Most health care providers are dependent on the proprietary name to identify the product rather than utilizing the established name for product recognition.

Prempro differs, in that the active ingredients are well established and the product can clearly be identified by the established name. OPDRA believes that the addition of another proprietary name will further complicate matters.

III. RECOMMENDATIONS

The applicant has failed to provide persuasive evidence to minimize OPDRA's concern with regard to the addition of a new proprietary name for the lower strengths of this combination product. OPDRA recommends the continued use of the previously approved proprietary name PREMPRO for the new strengths with the addition of the strength modifiers as outlined above.

OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Holquist, R.Ph. at 301-827-3244.

Carol Holquist, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

APPEARS THIS WAY
ON ORIGINAL

/s/

Carol Holquist
1/4/01 04:05:44 PM
MEDICAL OFFICER

Jerry Phillips
1/5/01 10:47:30 AM
DIRECTOR

this document has been previously signed off

Martin Himmel
1/9/01 01:37:51 PM
MEDICAL OFFICER

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.

Status of Advertising

No advertising material has been submitted. It is requested in the approval letter.

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, [redacted] means that all six tablets at Stage 1 cannot be less than [redacted] .herefore, a specification of Not Less Than [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

APPEARS THIS WAY
ON ORIGINAL

/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

12 April 2001

Conjugated Estrogens/MPA Low Dose
Response to FDA

Question 2:
Your proposed medroxyprogesterone acetate *in vitro* dissolution method via USP disintegration apparatus is acceptable on an interim basis. The recommended medroxyprogesterone acetate specification for the 0.45 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate and 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate oral tablets are as follows:

Time	% Medroxyprogesterone Acetate Released
30 minutes	Not less [redacted]

Please develop medroxyprogesterone acetate dissolution methods via the USP *in vitro* dissolution apparatuses (basket and paddle) for the 0.45 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate and 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate tablets as well as the other approved strengths of conjugated estrogens and medroxyprogesterone acetate tablets. The final dissolution specifications for the medroxyprogesterone acetate components of the 0.45 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate and 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate tablets will be based on data via the USP *in vitro* dissolution apparatus.

Response:
Wyeth-Ayerst agrees to accept the FDA's proposal to change the dissolution sampling time from 45 to 30 minutes. Note also that the current proposed NDA dissolution value of [redacted] is now expressed as Not less than [redacted], in agreement with the FDA proposal. (An [redacted] (Q) value corresponds to a USP <711> Stage 1 acceptance criterion of not less than [redacted]. The revised NDA specification pages attached in the response to Question 1 incorporate this change.

Wyeth-Ayerst has in the past attempted to devise dissolution methodology using USP <711> Apparatus 1 or 2. The intent of the initial study was to provide a method which reflected the immediate release characteristics of the comparator market product MPA tablet. Conventional USP apparatus yielded dissolution results up to 12 hours, having no relation to *in vivo* performance of the product. Wyeth-Ayerst has further investigated the use of USP Apparatus 2 using [redacted] (A technical drawing of a [redacted] is provided following this response.) Preliminary work indicates that the use of this standard USP dissolution method will provide an appropriate dissolution method, when [redacted] are employed. The company commits to conduct a dissolution feasibility study and to provide to the FDA the following information approximately 4 months after approval of this supplemental application:

1. A copy or a summary of the new analytical dissolution method for the MPA component of the CE/MPA 0.45/1.5 mg combination tablet.
2. Preliminary dissolution data.

Amended Patent / E. .sivity Information

1)	Active ingredent(s)	Conjugated estrogens and *medroxyprogesterone acetate*
2)	Strength(s)	1. 0.45 mg *conjugated estrogens* plus 1.5 mg medroxyprogesterone acetate -- administered continuously 2. 0.3 mg conjugated estrogens plus 1.5 mg *medroxyprogesterone acetate* -- administered continuously
3)	Trade Name	To be determined
4)	Dosage Form	Tablets, Oral
5)	Applicant Firm Name	Wyeth-Ayerst Laboratories
6)	NDA Number	20-527
7)	Approval Date	to be determined
8)	Exclusivity - Date first ANDA could be submitted or approved and length of exclusivity period	Pursuant to Section 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii) of the Federal Food, Drug, and Cosmetic Act, no ANDA may be approved with an effective date which is prior to 3 years after the date of approval of this NDA Supplement
9)	Applicable patent numbers and expiration date of each	• U.S. Patent No. Re. 36,247 Expiration Date: May 2, 2006 • U.S. Patent No. 5,547,948 Expiration Date: January 17, 2015 • U.S. Patent No. 5,210,081 Expiration Date: February 26, 2012

EXCLUSIVITY SUMMARY for NDA # 20-527 SUPPL # 017

Trade Name Prempro Generic Name conjugated estrogens/medroxyprogesterone tablets 0.45/1.5 mg
Applicant Name Wyeth-Ayerst Laboratories HFD-580

Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA? YES/___/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

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

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

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /_X__/ NO /__/

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

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name _____

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 4-782 Premarin

NDA # 20-363 Prempro/Premphase

NDA # 11-839 Provera

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or

2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

. If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X__/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # Protocol No. 713B-309-US (the HOPE study)

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical

investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

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

Investigation #1	YES /_ _/	NO /_X__/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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

Investigation Study # Protocol No. 713B-309-US(the HOPE study)

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a). For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

YES /_X_/ | NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ | NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ | NO /___/ Explain _____

_____ | _____

_____ | _____

Investigation

YES /___/ Expl

_____

_____

(c) Notwiths
there oth
should nc
sponsored
used as t
rights to
the drug)
sponsore
conducte

___/___/___ ___/___/___

If yes, expl :

_____

_____

Diane Moore, _____
Signature of Prepar
Date
Title: Regulatory Pr

Dr. Susan Allen, M.D.
Signature of Office

cc:
Archival NDA 20-52
HFD-580/Division Fi
HFD-580/D.Moore
HFD-093/Mary Ann Ho

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

APPEARS THIS WAY
ON ORIGINAL

/s/

Diane V. Moore
4/13/01 03:49:15 PM
CSO

Susan Allen
4/13/01 04:15:37 PM
MEDICAL OFFICER

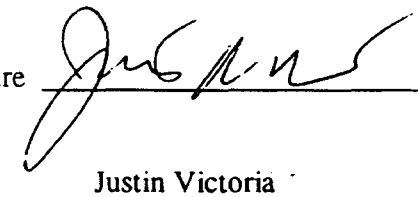
APPEARS THIS WAY
ON ORIGINAL

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

Labeling Supplement for Lower Doses

1.5 Item 16: Certification Required by the Generic Drug Enforcement Act of 1992

The undersigned certifies that Wyeth-Ayerst did not and will not knowingly use in any capacity the services of any person debarred under subsection (a) or (b) [section 306 (a) or (b)] of the Generic Drug Enforcement Act of 1992 in connection with NDA No. 20-527 for Conjugated Estrogens and Medroxyprogesterone Acetate Combination Tablets.

Signature 

Justin Victoria
Vice President, Worldwide Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

Date: January 29, 2001

From: Kim Colangelo
Senior Regulatory Associate
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 20-527/S-017
NDA 4-782/S-115

I have reviewed the financial disclosure information submitted by Wyeth-Ayerst Laboratories in support of their supplemental NDAs, NDA 20-527/S-017 and NDA 4-782/S-115.

One study was conducted to support the safety and efficacy of Prempro/Premphase (NDA 20-527/S-017) and Premarin (NDA 4-782/S-115) for the t —— vasomotor symptoms associated with menopause — vulvar and vaginal atrophy. The study number and the results of the review of financial disclosure documents are summarized below:

Study Number/Title	Study Status	Financial Disclosure Review
Study 309-US, "Health and Osteoporosis, Progestin and Estrogen Study"	Ongoing as of February 2, 1999	Appropriate documentation received, financial disclosure does not impact study outcome

Documents Reviewed:

- Financial Certification and Disclosure Information submitted June 15, 2000 (NDA 20-527/S-017) and July 31, 2000 (NDA 4-782/S-115)
- Facsimile to Ms. Lana Pauls dated July 19, 2000 containing number of patients per site with non-compliant investigators (attached)
- Financial Certification and Disclosure Information submitted November 22, 2000 (NDA 20-527/S-017 and NDA 4-782/S-115)

In addition, clarification of several points in these documents was requested via telephone on January 25, 2001. Verbal response was received from the sponsor on January 26, 2001. Specifically:

1. Regarding the July 19, 2000 facsimile:
   a) The number of patients enrolled per subinvestigator is actually per site. For example, a total of 16 patients were seen at Site 58, which had six non-compliant subinvestigators, not 16 patients per subinvestigator.
   b) The number of patients at Site 13 (Principal Investigator Reindollar) was six, not 13 as listed for
   c) The number of patients analyzed was 2,673. The term "analyzed" is equivalent to the terms "active" and "completed" used in individual financial disclosure statements.

d) The number of patients enrolled was 2,805.

2. Regarding the October 17, 2000 submission
   a [redacted] (sub)investigator in an August 30, 2000, submission, which is why his name did not appear on the initial certification dated March 17, 2000.

Study 309-US

There were 323 principal and subinvestigators (investigators) in this trial. Seventeen investigators at ten sites enrolling 16.0% of the total patients enrolled did not submit financial certification or disclosure documents to the sponsor. Of the remaining investigators who complied, five had disclosable information. They are summarized as follows:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

The sponsor employed the following mechanisms in an attempt to obtain Financial Disclosure forms from investigators:

- telephone calls to the sites and/or universities requesting additional information on the investigators,
- faxes to sites which indicated that a forwarding address was available,
- faxes to locations found as a result of Internet searches,
- Medical Monitor contact from previous professional associations,
- Internet searches of personnel directories of professional organizations such as ACOG, and
- e-mails to sites where addresses could be found.

Conclusion:

Adequate documentation was submitted to comply with 21 CFR 54. The sponsor has acted with due diligence in attempting to obtain documentation from non-compliant investigators and the rate of return is acceptable. The information disclosed is not significant enough to impact the study outcome.

FACSIMILE TRANSMISSION
WYETH-AYERST RESEARCH
170 RADNOR-CHESTER ROAD
ST. DAVIDS, PA 19087

Telefax Number: (610) 964-5973

DATE: *July 19, 2000*

TO: ***Lana Pauls, Associate Director***
Division of Reproductive and Urologic Drug Products

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

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

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

Re. *NDA No. 20-527 S-017*

Lana,

As you requested this morning, I am providing you with a table that lists investigators that did not provide Financial Disclosure forms, their site [(site number (principle investigator)] and the number of patients enrolled at the site. In addition the total number of patients that were analyzed is given. See the attached table.

If you have any questions, please contact me at the above referenced telephone number.

Regards,

JoAnne M. Bissinger
Manager, Worldwide Regulatory Affairs

DRUDP.fax

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

Investigator	Site # (Principe Investigator)	No. of Patient
	58 (Mezitis)	16
	58 (Mezitis)	16
	58 (Mezitis)	16
	58 (Mezitis)	16
	25 (Moghissi)	77
	25 (Moghissi)	77
	57 (Lobo)	65
	04 (Polan)	40
	62 (Dumesic)	48
	34 (Calkins)	72
	33 (Ravnikar)	03
	46 (Kessel)	39
	17 (Fossum)	45
	46 (Kessel)	39
	26 (Kubik)	19
	22 (Homesley)	21
	44 (Utian)	113
	26 (Kubik)	19
	29 (Pinkerton)	64
	25 (Moghissi)	77
	20 (Harrington)	14
	58 (Mezitis)	16
	46 (Kessel)	39
	57 (Lobo)	65
	61 (Liu)	29
	03 (Bachmann)	23
	62 (Dumesic)	48
	06 (Bush)	46
	58 (Mezitis)	16
	04 (Polan)	40
	58 (Mezitis)	16
	35 (Schaff)	28
	61 (Liu)	29
	13 (Reindollar)	06
	02 (Archer)	73
	06 (Bush)	46
	37 (Shoupe)	95
	17 (Fossum)	45
	13 (Reindollar)	13

2,673 patients were analyzed

/s/

Kim Colangelo
2/5/01 11:28:38 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-527/S-017

INFORMATION REQUEST LETTER

Wyeth-Ayerst Research
Attention: Joseph S. Sonk, Ph.D.
Assistant Vice President, Worldwide Regulatory Affairs
Global Therapeutic Area Head, Women's Healthcare
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Sonk:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prempro™ (conjugated estrogens/medroxyprogesterone acetate tablets) and Premphase® (conjugated estrogens/medroxyprogesterone acetate tablets).

We also refer to your submission dated April 30, 2001, containing questions regarding the Agency's April 13, 2001 Approvable Letter.

We have reviewed the referenced material and have the following comments.

Question 1:
In the **Clinical Studies** subsection, under Information Regarding Effects on Vasomotor Symptoms, why did the Division delete the figure entitled "

Response to Question 1:
A table showing the mean numbers of hot flushes and the mean change from baseline replaced the proposed figure. Clinical trial results at Weeks 4, 8, and 12 are shown for the 0.625 mg CE/2.5 mg MPA, 0.45 mg CE/1.5 mg MPA and placebo treatment groups. The tabular format provides more complete clinical trial findings for review by the healthcare provider than the proposed figure, and is the desired depiction for this information.

Question 2.
In the **Clinical Studies** subsection on Vulvar and Vaginal Atrophy, why was the table deleted from this section?

Response to Question 2:
The abbreviated table, as proposed, does not add information to the text description of the clinical trial results regarding the estrogenic effects on maturation indexes. If you prefer to retain a table showing the maturation index results, such a table should represent the data provided to the

Division on March 22, 2001, showing maturation index results at Cycles 6 and 13 for superficial, intermediate and parabasal cells for the Prempro 0.625 mg CE/2.5 mg MPA, Prempro 0.45 mg CE/1.5 mg MPA, and placebo treatment groups.

Question 3:
In the **Clinical Studies** subsection, on the Effects on the Endometrium, Table 5, "Incidence of Endometrial Hyperplasia After One Year of Treatment." What are the reason(s) for the references to [redacted] Wyeth-Ayerst relayed that the prescribing physician(s) wants to know how the individual pathologists have cited these cases in order to more completely understand these data.

Response to Question 3:

[redacted]

Question 4:
In the **Clinical Studies** section on the Effects on the Endometrium, in Table 5

[redacted]

Response to Question 4:
From the pathologist's reports which were provided in the NDA submission, the final diagnosis for Subject 30912-0049 in the 0.45 mg CE/1.5 mg MPA treatment group was reclassified as an endometrial adenocarcinoma in a polyp by the clinical review team (the reviewer, a board-certified pathologist in the Division, and the medical team leader) based on the information submitted. The findings in this case are as follows:

Subject # 30912-0049 in Group E (0.45 mg CE/1.5 mg MPA)

Final prestudy endometrial biopsy diagnosis=	Endometrial tissue (other) i.e., benign, inactive or atrophhic fragments of endometrial epithelium, glands, stroma, etc.

Cycle 7 endometrial biopsy on 1/12/99	
Pathologist 1=	Endometrial malignancy; well-differentiated endometrial adenocarcinoma involving endometrial polyp.
Pathologist 2=	Complex hyperplasia with atypia; hyperplastic focus appears to be in polyp.
Pathologist 3=	Endometrial malignancy; Grade I adenocarcinoma (endometroiod/mucinous) in a polyp, mucinous (including intestinal) metaplasia, ciliary change.
Subject withdrawn from the study on 1/25/99	
Repeat endometrial biopsy on 1/26/99	
Pathologist 1=	Complex hyperplasia with atypia; a. benign cervical and endometrial fragments b. Complex hyperplasia with atypia, focal
Pathologist 2=	Complex hyperplasia with atypia; a. focal residual atypical hyperplasia b. fragments of benign endocervix and endometrium
Total abdominal hysterectomy on 4/20/99	
"Out of study" surgical pathology report=	Weakly proliferative endometrium, leiomyoma and adenomyosis, no evidence of hyperplasia or carcinoma.

In this case, the majority decision (two of the three pathologists) is well-differentiated adenocarcinoma in a polyp, based on the initial Cycle 7 endometrial biopsy readings.

Question 5:
In the **Clinical Studies** sub

Response to Question 5:
The utilization of a cumulative amenorrhea graph showing all enrolled subjects is now standard in current HRT labeling.

Number of Pages Redacted 2

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

/s/

Jeanine Best
5/11/01 08:15:32 AM
signing for

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ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-527/S-017

INFORMATION REQUEST LETTER

Wyeth-Ayerst Laboratories
Attention: Joseph S. Sonk, Ph.D.
Senior Director U.S. Regulatory Affairs
PO Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Sonk:

Please refer to your supplemental new drug application dated June 15, 2000, received June 15, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Conjugated Estrogens (CE) and Medroxyprogesterone Acetate (MPA) Combination Tablets (0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA).

We are reviewing the submitted draft labeling from your submissions and have the following comments and information requests. Revisions have been incorporated directly into the enclosed Physician Package Insert. Additions have been noted with double underlining, deletions have been noted as ~~strikeouts~~. Additional comments requiring response are denoted in **14 point** bold face type.

We have the following comments in regard to your proposal for a new proprietary name for the two new lower strength tablets:

1. Dosage clarifications between physicians and pharmacists are not uncommon with any drug product especially when multiple strengths are involved. Although dosage clarifications can be considered an inconvenience, they can also provide the opportunity of a positive intervention, in that it allows the pharmacist another chance to verify the correct drug with the prescriber prior to dispensing.

We believe that the addition of the new lower strengths would require physicians to practice better prescribing habits with this drug product. Physicians would have to include the dosage of each ingredient on the prescription or they will be overwhelmed with telephone calls from other health care practitioners regarding strength clarification.

We believe that launching the new low dose CE/MPA product(s) under a new tradename is misleading to healthcare professionals, in that it implies a different product. Launching under the existing PREMPRO tradename, would require physicians to designate the CE dosage and the MPA dosage when prescribing the desired dose. This would eliminate the past confusion demonstrated when these descriptors were missing from the ordering process. We recommend

including the labeled amount of each active ingredient in conjunction with the proprietary name. We also recommend differentiating the product strengths with the use of contrasting color, boxing or some other means.

We recognize that separate tradenames for products with the same active ingredients have been approved by the Agency in the past. However, new policies and procedures involving proprietary name reviews have been implemented since approval of the products referenced in your NDA. The Agency routinely discourages the addition of a separate tradename for products containing the same active ingredients for the following reasons:

1. The creation of another proprietary name for a new strength or indication adds unnecessarily to the growing number of tradenames in the United States, thus creating additional safety concerns.

2. We believe that having two tradenames by the same manufacturer, for the same bioequivalent drug product is misleading to health care professionals, in that it implies a different product.

In addition, it is the policy of the Center that OPDRA will no longer recommend approval of different proprietary names by the same applicant or manufacturer for products that are essentially identical unless there is a public health risk or stigma associated with the use of the drug product. The Agency is concerned with the proliferation of proprietary names for the following reasons:

1. Overdose: Practictioners may become confused and not understand that the two products (with two different trade names) are identical. This may increase the risk of a patient being prescribed the same drug product by different physicians, resulting in an overdose.

2. Medication Errors: The creation of a new proprietary name for a new strength of an essentially identical drug product adds unnecessarily to the growing number of proprietary names in the United States. This proliferation of numerous proprietary names may increase the likelihood of occurrence of medication errors resulting in patient injury due to sound-alike and/or look-alike confusion between products.

3. Confusion/Misleading: Trivialization of the adverse events and risks associated with the use of different proprietary names for the same active moiety. Patients may be falsely assured that the medication does not carry significant risks because the FDA has allowed its use for a relatively benign condition.

4. False Implication: The separate proprietary name implies that there is a unique indication that is deserving of a separate name, when in fact this is not true.

5. Management of ADE: The increasing complexity to manage (regulatory) reports of adverse drug events associated with one active ingredient with two or more proprietary names.

6. Pharmacy Burden: The proliferation of numerous proprietary names for the same active ingredient places an inventory and storage burden on pharmacies and pharmacists.

We believe there are no public health risks or stigmas associated with the use of one proprietary name for this drug product. Therefore, the safe use of this product is best managed under one proprietary name.

We recommend the continued use of the previously approved proprietary name PREMPRO for the new strengths with the addition of the strength modifiers.
We need your prompt written response to continue our evaluation of your supplemental application.

If you have any questions, call Diane Moore, BS, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 187

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/s/

Jeanine Best
4/5/01 11:40:15 AM
igning for Terri Rumble, CPMS

APPEARS THIS WAY
ON ORIGINAL

NDA 20527/S-017

PRIOR APPROVAL SUPPLEMENT

Wyeth-Ayerst Laboratories
Attention: Joseph S. Sonk, Ph.D.
Senior Director U.S. Regulatory Affairs
PO Box 8299
Philadelphia, PA 19101-8299

JUN 19 2000

Dear Dr. Sonk:

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

Name of Drug Product:	Conjugated Estrogens (CE) and Medroxyprogesterone Acetate (MPA) Combination Tablets (0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA)
NDA Number:	20-527
Supplement Number:	S-017
Therapeutic Classification:	Standard (S)
Date of Supplement:	June 15, 2000
Date of Receipt:	June 15, 2000

This supplement proposes the following change(s): The addition 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 treatment of vulvar and vaginal atrophy.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 14, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 15, 2001 and the secondary user fee goal date will be June 15, 2001.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Diane Moore, BS, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/ 6/19/00

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20527/S-017
HFD-580/Div. Files
HFD-580/D.Moore/TRumble
HFD-580/SAllen/MMann/SSlaughter/Tvandervlugt
HFD-580/MRhee/AJordan/Aparekh/LKammerman
DISTRICT OFFICE

/S/ 6/19/00

Drafted by: dm/June 19, 2000
Initialed by: TRumble 6.19.00
final: June 19, 2000
filename: N20527S017AK.doc

PRIOR APPROVAL SUPPLEMENT ACKNOWLEDGEMENT (AC)

Wyeth

February 28, 2003

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

Daniel Shames, M.D., Director
Division of Reproductive & Urologic Drug Products
HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Attn: Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

General Correspondence
Information Package For CMC Meeting / Teleconference

Dear Dr. Shames:

Reference is made to NDA No. 20-527/S-017 for Prempro™ (conjugated estrogens/medroxyprogesterone acetate tablets), Premphase® (conjugated estrogens / medroxyprogesterone acetate tablets) submitted to DRUDP on June 15, 2000 for the use of conjugated estrogens (CE) and Medroxyprogesterone Acetate (MPA) (CE 0.45 mg/MPA 1.5 mg) in a continuous combined regimen for the treatment of moderate to severe vasomotor symptoms and [redacted] vulvar and vaginal atrophy associated with menopause.

Further reference is made to the Agency's Approvable Letter of April 13, 2001 and Wyeth's complete response to the Approvable Letter on September 11, 2002.

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

OC RECOMMENDATION	23-OCT-2002	ACCEPTABLE	DAMBROGIOJ
		BASED ON PROFILE	

Profile: TTR OAI Status: POTENTIAL OAI

Estab. Comment: DRUG PRODUCT MANUFACTURER. (on 30-JUN-2000 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision	Creator
SUBMITTED TO OC	30-JUN-2000				LINDAV
SUBMITTED TO DO	03-JUL-2000	10D			DAMBROGIOJ
DO RECOMMENDATION	06-JUL-2000			ACCEPTABLE	JPODSADO
				BASED ON FILE REVIEW	
OC RECOMMENDATION	07-JUL-2000			ACCEPTABLE	FERGUSONS
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	23-OCT-2002				POPES
SUBMITTED TO DO	23-OCT-2002	10D			DAMBROGIOJ
DO RECOMMENDATION	31-OCT-2002			WITHHOLD	JPODSADO
				PREVIOUS DEVIATIONS PERSIST	

[redacted]

[redacted]

OC RECOMMENDATION	03-FEB-2003	ACCEPTABLE	WOODSR
		BASED ON PROFILE	

THIS CDER/OC ACCEPTABLE RECOMMENDATION ONLY APPLIES TO LOW DOSE STRENGTHS OF WYETH'SQUA PREMPRO (CONJUGATED ESTROGENS/MEDROXYPROGESTERONE ACETATE TABLET) THAT ARE PART OF THE FOLLOWING APPLICATIONS:

[redacted] MEDROXYPROGESTERONE ACETATE (MPA); GOAL DATE OF