CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-527/S-017

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

TIME SENSITIVE PATENT INFORMATION PURSUANT TO 21 C.F.R. 314.53
for NDA 20-527

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	To be determined
Active Ingredient(s):	conjugated estrogens and medroxyprogesterone acetate
Strength(s):	(1) conjugated estrogens (0.45 mg) and medroxyprogesterone acetate (1.5 mg) combination tablet - administered continuously. (2) conjugated estrogens (0.3 mg) and medroxyprogesterone acetate (1.5 mg) combination tablet - administered continuously.
Dosage Form:	Tablets, Oral
Approval Date:	To be determined

A. Information for each individual patent:

US Patent Number:	Re. 36,247
Expiration Date:	May 2, 2006
Type of Patent:	Method of Use - menopausal and postmenopausal disorders (including vasomotor symptoms associated with menopause, and vulvar and vaginal atrophy) and osteoporosis.
Patent Owner:	Pre Jay Holdings Ltd; WOCO Investments Ltd.
US Agent:	American Home Products Corp., parent company of the Applicant, is the exclusive licensee under the patent.

US Patent Number:	5,547,948
Expiration Date:	January 17, 2015
Type of Patent:	Drug Product (Composition/Formulation)
Patent Owner:	American Home Products Corp., parent company of the Applicant

US Patent Number:	5,210,081
Expiration Date:	February 26, 2012
Type of Patent:	Drug Substance (Active Ingredient) - covers a sodium salt of delta-8,9-dehydroestrone-3-sulfate, a drug substance (ingredient) that is an active component of the product described herein.
Patent Owner:	American Home Products Corp., parent company of the Applicant

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B. Declaration statement for listed patents which have Compostion/Formulation or Method of Use claims:

The undersigned declares that the above stated US Patent No. Re. 36,247 covers the method of use of the product described herein. This product is the subject of this application for which approval is being sought.

The undersigned declares that the above stated U.S. Patent No. 5,547,948 covers the formulation of the product described herein. This product is the subject of this application for which approval is being sought.

WYETH-AYERST LABORATORIES

By: 

Arnold S. Milowsky, Ph.D.
Senior Patent Attorney
Date: 4/13/00

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

Wyeth

FACSIMILE

Date: 3/12/03

Number of pages (including cover): 2

To: Ms. M. Kober
Telephone:
Fax: 301 827 4267 ~~87~~ 72
Urgent For your review

From: Jennifer D. Norman
Department: Worldwide Regulatory Affairs
Telephone: 484 865 3749
Fax: 484 865 9214

☐ ☐ ☐ Please reply asap ☐ Please comment

Remarks:

Ms. Kober:

As per our discussion at 4 pm, we have added the pointer "(See Dosage and Administration)" in the Indications and Usage section at the end of Indication #3 – Prevention of postmenopausal osteoporosis. Please see attached revision in writing.
Thank you

Jennifer Norman

Jennifer Norman

APPEARS THIS WAY
ON ORIGINAL

Table 10. RELATIVE AND ABSOLUTE RISK SEEN IN THE PREMPRO SUBSTUDY OF WHI[a]

Event[c]	Relative Risk PREMPRO vs Placebo at 5.2 Years (95% CI*)	Placebo n = 8102	PREMPRO n = 8506
		Absolute Risk per 10,000 Person-years	
CHD events	1.29 (1.02-1.63)	30	37
Non-fatal MI	*1.32 (1.02-1.72)*	*23*	*30*
CHD death	*1.18 (0.70-1.97)*	*6*	*7*
Invasive breast cancer[b]	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global Index[c]	1.15 (1.03-1.28)	151	170
Deep vein thrombosis[d]	2.07 (1.49-2.87)	13	26
Vertebral fractures[d]	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures[d]	0.77 (0.69-0.86)	170	131

a: Adapted from JAMA, 2002; 288:321-333

b: Includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer

c: A subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.

d: Not included in Global Index.

*: Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

For those outcomes included in the "global index", absolute excess risks per 10,000 person-years in the group treated with PREMPRO were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the "global index" was 19 per 10,000 person-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS**.)

INDICATIONS AND USAGE

PREMPRO or PREMPHASE therapy is indicated in women who have a uterus for the:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.

2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

3. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered. (See DOSAGE AND ADMINISTRATION.)

NDA SUPPL AMENDMENT

DUPLICATE

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

Worldwide Regulatory Affairs

Wyeth

March 6, 2003

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

Daniel Shames, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Fishers Document Control Room 8B-45
5600 Fishers Lane
Rockville, MD 20857

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. This sNDA supports 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 treatment of vulvar and vaginal atrophy associated with menopause.

Further reference is made to the Agency's approvable letter of April 13, 2001 and the recent teleconference on February 6, 2003 with representatives from DRUDP and Wyeth. The purpose of the teleconference on February 6, 2003, requested by the Agency, was to review the Agency's comments concerning text specific to the HOPE study contained in the proposed Prempro 0.45 mg/ 1.5mg labeling provided to Wyeth via E-mail on February 5, 2003.

The purpose of this submission is to provide proposed labeling for Prempro 0.45 mg/ 1.5 mg for the treatment of moderate to severe vasomotor symptoms and treatment of vulvar and vaginal atrophy associated with menopause. The revisions made by the Agency in the February 5, 2003 proposed labeling, which reflect the January 8, 2003 approved labeling for Prempro/Premphase marketed product formulations, have been incorporated into the proposed Prempro 0.45 mg/1.5 mg labeling. Only those revisions to text that are specific to the HOPE study are summarized below.

Number of Pages Redacted 3

❖❖❖

Draft Labeling
(not releasable

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

Worldwide Regulatory Affairs, CMC

Wyeth

March 6, 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.

Additional reference is made to the submission of February 28, 2003 which provided an Information Package to support Wyeth's proposal and teleconference on March 5, 2003.

In light of our March 5, 2003 teleconference the purpose of this correspondence is to clarify our proposal with regards to the immediate action relative to dissolution testing at the 5 hours timepoint. We propose an interim in-process specification at the active filled color polished stage to be — and an interim product release and shelf life specification at the branded finished tablet stage of —

Additionally we intend to perform dissolution surveillance on every packaged lot according to the attached, revised Dissolution Surveillance Program proposal.

During our March 5, 2003 teleconference the Agency requested the timeframe between the color polished tablet stage manufactured in Rouses Point and the packaging of the branded finished product in Puerto Rico. An approximate time span for this is 25-55 days.

We request confirmation that this proposal is acceptable.

Wyeth appreciates the responsiveness of the Agency in scheduling the March 5, 2003 teleconference prior to the User Fee Date of March 12, 2003.

We trust that you will find this submission satisfactory. If you have any questions regarding this submission please contact the undersigned at Tel: (484) 865-7983 or Fax: (484) 865-0028.

Regards,
Wyeth Pharmaceuticals, Inc.

Frederick A Golec Jr RPh.D. 3/6/03

Frederick A. Golec, Jr., Ph.D.
Director
Worldwide Regulatory Affairs, CMC

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

Worldwide Regulatory Affairs, CMC

Wyeth

March 5, 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 —— 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.

Additional reference is made to the submission of February 28, 2003 which provided an Information Package to support Wyeth's proposal and teleconference on March 5, 2003.

In light of our March 5, 2003 teleconference the purpose of this correspondence is to clarify our proposal with regards to the immediate action relative to dissolution testing at the 5 hours timepoint. We propose an in-process specification at the active filled color polished stage to be —— and a product release and shelf life specification at the branded finished tablet stage of ——

Additionally we intend to perform dissolution surveillance on every packaged lot according to the attached, revised Dissolution Surveillance Program proposal.

During our March 5, 2003 teleconference the Agency requested the timeframe between the color polished tablet stage manufactured in Rouses Point and the packaging of the branded finished product in Puerto Rico. An approximate time span for this is 25-55 days.

We request confirmation that this proposal is acceptable.

Wyeth appreciates the responsiveness of the Agency in scheduling the March 5, 2003 teleconference prior to the User Fee Date of March 12, 2003.

We trust that you will find this submission satisfactory. If you have any questions regarding this submission please contact the undersigned at Tel: (484) 865-7983 or Fax: (484) 865-0028.

Regards,
Wyeth Pharmaceuticals, Inc.

Frederick A Golec Jr PhD 3/5/03

Frederick A. Golec, Jr., Ph.D.
Director
Worldwide Regulatory Affairs, CMC

On February 10, 2003 Wyeth requested a meeting to discuss issues concerning the dissolution of the low dose CE 0.45 mg/MPA 1.5 mg tablet. As stated in that correspondence, Wyeth has continued efforts to study dissolution parameters. Following a decision to add a number of in-process controls and revalidate the process, tests showed a OOS finding for one of the three dissolution time points, i.e. 5 hour time point, that fell outside the previously agreed approvable specification.

The purpose of this submission is to confirm that a teleconference has been scheduled for March 5, 2003 at 3:00 - 4:00 p.m., and to provide an Information Package to support Wyeth's proposal and teleconference.

As stated in the attached, Wyeth proposes and seeks concurrence on immediate, near term, and long term actions. With regard to the immediate actions, Wyeth seeks permission to , as described in the attached materials. This immediate action has bearing on the review of this supplement, as FDA's concurrence on the proposed interim specification would be a prerequisite for the approval of this application. Wyeth believes the setting of the interim specification is necessary for the successful and timely launch of this low dose product.

The immediate action would be complemented by additional actions, including near term work for additional and improved in-process controls at the sealed core and filled core stages of conjugated estrogens tablet manufacture to meet tightened specifications at the time of completion of manufacture, and long term work to develop a new formulation for the various strengths of Premarin® tablets that can be provided for development activities to identify the CE/MPA version of the single entity product. In addition Wyeth proposes a Dissolution Surveillance program for the 0.45mg/1.5mg and CE/MPA tablets.

The Information Package contains:

Attachment 1 contains the agenda, list of Wyeth attendees and a summary with specific questions to be addressed at the teleconference.

Attachment 2 contains the Technical Portion of the Information Package. This is a summary of relevant information from Premarin® tablet revalidation studies, dissolution findings for CE 0.45 mg/MPA 1.5 mg revalidation batches, results of investigations into the low Conjugated Estrogens dissolution values at 5 hours for the revalidation batches, conclusions and the actions Wyeth is taking to address the issue. Also included is a proposed Dissolution Surveillance program.

Wyeth appreciates the responsiveness of the Agency in scheduling the March 5, 2003 teleconference prior to the User Fee Date of March 12, 2003.

We trust that you will find this submission satisfactory. If you have any questions regarding this submission please contact the undersigned at Tel: (484) 865-7983 or Fax: (484) 865-0028.

Regards,
Wyeth Pharmaceuticals, Inc.

Frederick A Golec Jr PhD 2/28/03

Frederick A. Golec, Jr., Ph.D.
Director
Worldwide Regulatory Affairs, CMC

Attachments:

Desk Copy:
Dr. Ajaz Hussain (full copy)
Ms. Margaret Kober (full copy)
Dr. David Lin (full copy)
Dr. Sarah Pope (full copy)
Ms. Kassandra Sherrod (4 full copies)

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

Worldwide Regulatory Affairs

Wyeth

ORIGINAL

February 28, 2003

RECEIVED
MAR 03 2003
CDER

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 and Urologic Drug Products (HFD-580)
Fishers Document Control Room 8B-45
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA SUPPL AMENDMENT
SE2-017 - ISV

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).

The purpose of this submission is to provide Prempro™ 0.45 mg/1.5 mg trade carton artwork in response to a request made by Ms. Kassandra Sherrod, Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP), on February 26, 2003. Enclosed are five paper copies of the Prempro™ 0.45 mg/1.5 mg trade carton (UK23353-3). The same trade carton artwork was submitted as a pdf file to Ms. Sherrod on February 27, 2003 via electronic mail using secure messaging.

Should you have any questions, please contact the undersigned at (484) 865-3749.

Sincerely,

Jennifer D. Norman

Jennifer D. Norman, RPh
Associate Director
Worldwide Regulatory Affairs

Desk Copies: Ms. Kassandra Sherrod, DRUDP.

ORIGINAL

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

Worldwide Regulatory Affairs

Wyeth

September 11, 2002

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

SE2 017 B2
NDA SUPPL AMENDMENT

Daniel Shames, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Fisher's Building, Room 8B-45
5600 Fishers Lane
Rockville, MD 20857

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. This sNDA supports 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 ~~—~~ vulvar and vaginal atrophy associated with menopause. Further reference is made to the Agency's approvable letter of April 13, 2001.

The purpose of this submission is to provide a complete response to the approvable letter of April 13, 2001 for NDA 20-527/S-017 as agreed to with Ms. Dornette Spell Lesane on August 14 and 19, 2002.

1. **Manufacturing facility** - With regard to the Guayama, Puerto Rico manufacturing facility and reference to the deficiencies noted by the inspector, subsequent to receiving the April 13, 2001 approvable letter, the facility was inspected by the Agency in March 2002 and has been found to be in cGMP compliance.
2. **Final Printed Labeling** – Reference is made to our submission of revised proposed labeling for Prempro, CE 0.45 mg / MPA 1.5 mg, as an amendment to NDA 20-527/S-017, dated July 31, 2002 as part of the complete response to the approvable letter.

Wyeth

3. **Chemistry, Manufacturing & Controls (CMC)** – Reference is made to the CMC Amendment to NDA 20-527/S-017 submitted to the Agency on August 2, 2002.
4. **Post-marketing study commitment** – We have committed to conduct a dissolution feasibility study and provide to FDA the following information approximately four months after the approval of this supplemental application :
   - A copy or summary of the new analytical dissolution method for the MPA component of the CE/MPA 0.45 mg /1.5 mg combination product.
   - Preliminary dissolution data.
5. **Safety Profile** – To satisfy this request, reference is made to NDA 20-527/S-024, submitted to the Agency on November 5, 2001, and the subsequent 4-month safety update submitted to the Agency on March 5, 2002. NDA 20-527/S-024 provided safety data from Years 1 and 2 of the HOPE Study. (NDA 20-527/S-017 contained safety data from Year 1 only of the HOPE Study.)

   For ease of review, the Clinical Study Report (CSR) 41303: *A Prospective, Double-Blind, Randomized Study of the Safety and Efficacy of Lower Doses of Premarin and Medroxyprogesterone Acetate in Postmenopausal Women: Final Report,* which contains a Safety Evaluation of the product, and the 4-month safety update to NDA 20-527/S-024, March 5, 2002, are enclosed on one CD ROM. The safety information contained in the enclosed reports is the most recent safety information on Prempro 0.45 mg/ 1.5 mg; no additional serious adverse events for Prempro 0.45 mg/ 1.5 mg, have been reported since the cut off date of January 31, 2002 for the 4-month safety update.
   - Significant changes or findings in the safety profile – There are no new significant changes to the safety profile for Prempro 0.45 mg /1.5 mg, including reports from the ongoing study, Protocol No. 0713X1-013-US, *A Prospective, Double-Blind, Randomized Study of the Effect of Premarin Vaginal Cream and Low-Dose Premarin/MPA on Dyspareunia, Atrophic Vaginitis, Sexual Function, Quality of Life and Genital Blood Flow,* submitted under [redacted], **Premarin (conjugated estrogens, USP) with Medroxyprogesterone Acetate (MPA).**
   - Premature Study Discontinuations – There were no new trends or patterns identified. The reasons for discontinuations are included in supportive tables ST8-2 and ST8-3 of the enclosed CSR 41303.

Wyeth

- Narrative Summaries for Serious Adverse Events or Deaths – Narrative summaries for patients who discontinued because of adverse events during year 2 of the HOPE study are included in the enclosed CSR 41303. There were no patient deaths in the year 2 metabolic substudy as detailed in CSR 41303.
- Changes in the incidence of common, but less serious, adverse events – There is no suggestion of a significant change in the incidence of common but less serious adverse events. Treatment emergent adverse events are included as supportive table ST10-7 in CSR 41303.
- Worldwide experience on the safety of this drug – CE 0.45 mg/MPA 1.5 mg is not yet marketed in any other countries.
- Foreign labeling – English translations of approved foreign labeling are included on the enclosed CD-ROM. CE 0.45 mg / MPA 1.5 mg has been approved in Australia, Chile, Finland, Iceland Netherlands, Portugal, and Switzerland.

As noted above, this submission constitutes our complete response to the approvable letter for NDA 20-527/S-017, dated April 13, 2001.

This amendment is provided as an electronic file. The approximate size of the submission is 58 megabytes and is contained on one (1) CD-ROM. All files were scanned for viruses using McAfee VirusScan, version 4.0.3a, and no viruses were detected. The electronic information is being submitted to the FDA/CDER Central Electronic File Room for loading onto the FDA network.

If you have any questions regarding this application, please contact the undersigned at (484) 865-3749 or Dr. Joseph S. Sonk at (484) 865-3740.

Sincerely,

Jennifer D. Norman

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

WYETH-AYERST RESEARCH

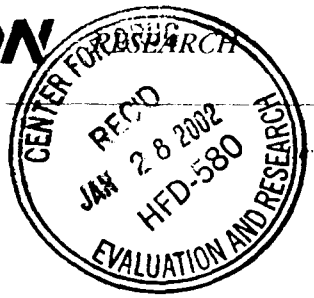
BOX 8299 • PHILADELPHIA, PA 19101-8299

WORLDWIDE REGULATORY AFFAIRS

A Division of American Home Products Corporation

ORIGINAL

SUPPL



January 25, 2002

NDA No. 20-527/S-017 Prempro™/Premphase® (conjugated estrogens/medroxyprogesterone acetate)
NDA No. 20-527/S-024 Prempro™/Premphase® (conjugated estrogens/medroxyprogesterone acetate)
NDA No. 21-396 Prempro™/Premphase® (conjugated estrogens/medroxyprogesterone acetate)

Daniel Shames, M.D., Acting 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

GENERAL CORRESPONDENCE

Dear Dr. Shames:

Reference is made to our approved New Drug Application No. 20-527 for Prempro™/Premphase® (conjugated estrogens/medroxyprogesterone acetate) Single Tablet, Supplement (S-017) submitted to this Application on June 15, 2000, Supplement (S-024) submitted to this Application on November 5, 2001, NDA No. 21-396 Prempro™/Premphase® (conjugated estrogens/medroxyprogesterone acetate), and the telephone contact with Ms. Diane Moore and Dr. David Lin on January 10, 2002.

Ms. Moore and Dr. Lin requested that Wyeth Ayerst provide correspondence that would cross-reference our recent above referenced submissions. We hereby provide the requested cross-reference information.

NDA 21-396 and NDA 20-527 Supplement 024 both contain identical Chemistry Manufacturing and Controls sections. The CMC sections for these submissions were copied from the CMC section of NDA 20-527 Supplement 017 and then updated with the current information that was filed in Amendments to NDA 20-527 Supplement 017. A chart of these Amendments to NDA 20-527 Supplement 017 has been attached for your convenience. The only differences between NDA 20-527 Supplement 017 and the other two submissions, NDA 21-396 and NDA 20-527 Supplement 024, are:

1. NDA 21-396 and NDA 20-527 Supplement 024 include a notation in the Stability section that the 24 month stability was completed prior to FDA's requested change in specifications, therefore Wyeth noted that all future testing would be performed under the new specification; and

2. NDA 21-396 and NDA 20-527 Supplement 024 include an updated chart in the Investigational Formulations section to include clinical study number 0713D2-312-JA.

If you have any questions, please contact the undersigned at (484) 865-3743 or Dr. Karel Bernady at (484) 865-3760.

Sincerely,

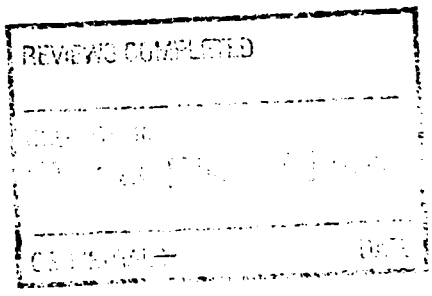
WYETH-AYERST LABORATORIES

Nirdosh Jagota, Ph.D.
Director
Worldwide Regulatory Affairs

Attachment

Desk Copy: Dr. David Lin (full copy)
Ms. Diane Moore (full copy)

APPEARS THIS WAY ON ORIGINAL



Number of Pages Redacted 3

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Draft Labeling
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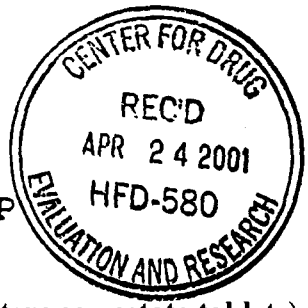
WWW.WYETH.COM

ORIGINAL

~~SUPPL NEW CORRESP~~

NDA SUPP AMEND



April 23, 2001

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

20e2-017-BL

Susan Allen, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
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) and Premphase® (conjugated estrogens/medroxyprogesterone acetate tablets) submitted to DRUDP on June 15, 2000. Reference is also made to the Agency's Approvable Letter faxed to Dr. Joseph Sonk (Wyeth-Ayerst) on April 13, 2001 and to the Agency's letter faxed to Ms. Jennifer Norman (Wyeth-Ayerst) on April 4, 2001.

Reference is also made to a telephone discussion between Mrs. Moore, the undersigned and Ms. Cynthia Davidson on April 16, 2001.

The purpose of this telephone conversation was to request the Reviewing Division's rationale for deletions to the draft HOPE labeling. In FDA's Approvable Letter of April 13th, the Wyeth-Ayerst suggestions for the revised labeling were struck out with no annotations. Ms. Moore relayed that the Medical Officer was not currently available, but that she (Ms. Moore) would take our questions to her when she returned. For the convenience of the Reviewer, we are providing Wyeth's questions in this submission.

Please note that the referenced pages from April 13th Action Letter are attached.

The clarifications requested of Ms. Moore were:

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

1. Clinical Studies, Section on the Effects on Vasomotor Symptoms. We asked for clarification as to why the FDA deleted the figure entitled '

2. Clinical Studies, Section on Vulvar and Vaginal Atrophy. We asked for clarification as to why the table was deleted.

3. Clinical Studies, Section on the Effects on the Endometrium, Table 5, '
We asked for the rationale for the references to the being stricken in their entirety from this table. We relayed that the prescribing physician wants to know how the individual pathologists have cited these cases.

4. Clinical Studies, Section on the Effects on the Endometrium, Table 5, "Incidence of
e asked the Division why the
. Ms. Moore noted that the medical officer determined that the diagnosis was We asked how the medical officer made the determination that the ' but and agreed this needed further discussion.

5. Clinical Studies, Section on Control of Bleeding, Figure, '
ınt

6. Warnings, Induction of malignant neoplasms, Endometrial cancer, second paragraph. The last sentence, '
is being deleted by the Division. We asked for clarification.

7. Warning, Induction of malignant neoplasms, Endometrial cancer, second paragraph. In the previous HOPE labeling revision provided by FDA to Wyeth on April 4, 2001 via fax, the fourth paragraph, '
" was deleted in its entirety by the FDA, including the statement that '
As such, the sentence in clarification number 6 is being requested for inclusion in the current second paragraph to address the deletion of the fourth paragraph in the previous revision of the April 4th fax.

8. We asked for the rationale for the deletion of this paragraph.

9. Precautions, Carcinogenesis, Mutagenesis and Impairment of Fertility, fourth paragraph. We asked for clarification for the FDA's deletion of the statement [redacted]

10. HOW SUPPLIED. The Wyeth draft labeling states, [redacted] ' We asked why this statement has changed to, "Store at 25°C (77°F)...[see USP Controlled Room Temperature]." We pointed out that this is not what is defined in the USP for Controlled Room temperature. Ms. Moore acknowledged that we do have a range approved now on our label for the other Premarin products, but that the statement requested is part of the process of standardizing the label.

If you have any questions regarding this submission, please contact the undersigned at at (610) 902-3740 or Ms. Davidson at (610) 902-3719.

Sincerely,

WYETH-AYERST LABORATORIES

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

Desk Copy: Ms. Diane Moore

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 20, 2001

To: Susan Allen

From: Joseph S. Sonk

Department: Worldwide Regulatory Affairs

Number of Pages (*including cover sheet):* 2

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

WYETH-AYERST RESEARCH

...N 8299 • PHILADELPHIA, PA 19101-8299 • (610) 902-3740 • FAX (610) 966-5953
...ENELSONK@WAR.WYETH.COM

Division of American Home Products Corporation

...ELSON, PhD
...ssociate Vice President
...Worldwide Regulatory Affairs

April 19, 2001

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

Susan Allen, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
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) and Premphase® (conjugated estrogens/medroxyprogesterone acetate tablets) submitted to DRUDP on June 15, 2000. Reference is also made to the Agency's Approvable Letter faxed to Dr. Joseph Sonk (Wyeth-Ayerst) on April 13, 2001.

Pursuant to 21 CFR 314.110, we intend to amend the application.

If you have any questions regarding this submission, please contact the undersigned at at (610) 902-3740 or Ms. Cynthia Davidson at (610) 902-3719.

Sincerely,

WYETH-AYERST LABORATORIES

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

JS:lf\013

WYETH-AYERST RESEARCH

April 12, 2001

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

ORIGINAL

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

SUPPL NEW CORRESP
017-NDC

Dear Dr. Allen:

Reference is made to NDA No. 20-527/S-017 for PREMPRO (conjugated estrogens/ medroxyprogesterone acetate tablets), and PREMPHASE (conjugated estrogens/ medroxyprogesterone acetate tablets) submitted to DRUDP on June 15, 2000

Reference is also made to discussions during April 9-11, 2001 between Mrs. Diane Moore of the Division ' me concerning the graphics contained on the container, pouch and carton labels. This was one of the jects contained in the Division's letter of April 4, 2001. During these discussions it was agreed that the container, pouch and carton labels, as submitted (example attached), can be used for the first 4 months of sales for this product.

Wyeth-Ayerst agrees that subsequent to the first 4 months of sales, the "line" between the trade name and established name will be removed, as will the graphic "swirl" in the right-hand bottom corner and the phrase "Nothing Else is "graphic swirl" " in the top left-hand corner. These representations will be removed from each panel so printed.

As noted to Mrs. Moore during our discussions, we would like to work with the Division to add back these graphic representations as soon as possible. We believe we will demonstrate to the Division's satisfaction that these graphics are routinely employed by our competitors and should be allowed for Wyeth-Ayerst as well.

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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: DRUDP: Mrs. Diane Moore, Project Manager

JSS:pd

Number of Pages Redacted 1

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Draft Labeling
(not releasable

WYETH-AYERST RESEARCH

ORIGINAL

April 12, 2001

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

NDA SUPP AMEND

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.

As requested, please find the attached safety report for this submission. Summary information from the report has been faxed to the Division this evening.

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

Sincerely,

WYETH-AYERST LABORATORIES

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

WYETH-AYERST RESEARCH

ORIGINAL

April 12, 2001

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

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

NDA SUPP AMEND

Dear Dr. Allen:

Reference is made to NDA No. 20-527/S-017 for PREMPRO (conjugated estrogens / medroxyprogesterone acetate tablets) and PREMPHASE (conjugated estrogens / medroxyprogesterone acetate tablets) submitted to DRUDP on June 15, 2000. Reference also is made to the Wyeth-Ayerst (W-A) submission of April 11, which was made in response to the Agency's Discipline Review Letter of April 4. Further reference is made to the telephone conferences between 2:30 and 5 PM with the Agency of April 11, 2001.

As stated by Wyeth-Ayerst during the teleconference, W-A believes that the dissolution specification for conjugated estrogens (CE) at 5 hours [redacted] proposed by W-A is appropriate since we believe the data submitted on April 11, 2001 supports this proposed range. Since we have agreed to the Division's proposed ranges, should an issue arise in the future, we look forward to the Division Chemists' support for prompt resolution in a mutually agreeable fashion.

In summary, Wyeth-Ayerst agrees to FDA's proposed specifications for CE dissolution. We appreciate FDA's commitment that the Agency is willing to revisit the CE specifications, supported with the expected additional data, after one year of approval.

Enclosed please find an amendment to the supplemental application S-017 in response to the agreements reached between the Agency and W-A on April 11, 2001. Wyeth-Ayerst, herein, submits following pages:

1. The revised NDA pages for sections 4.1.4.6.1 (specifications) and 4.1.4.7.3 (specifications as part of stability protocol).

2. Revised page 013 from the submission of April 11, 2001 with a correction of typographical error on line 3, paragraph 1 of Wyeth-Ayerst response. The revised description of MPA

TH 3462

Dissolution specification now states 'Not less [redacted]' which is consistent with NDA specification pages.

If you have any questions regarding this submission, please contact the undersigned at (610) 902-3743 or Dr. Joseph Sonk at (610) 902-3740.

Sincerely,

WYETH-AYERST LABORATORIES

Nirdosh Jagota, Ph.D.
Director
Worldwide Regulatory Affairs

Attachments

Desk Copy: Ms. Diane Moore
Dr. David Lin

U:\Premarin\20527 S017 FDA amend 041201.doc

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

FAX

Wyeth Ayerst Research
Worldwide Regulatory Affairs
170 Radnor-Chester Road
St. Davids, PA 19087

BC

.e April 12, 2001

Number of pages including cover sheet 12

To:	Ms. Diane Moore	From:	Cynthia Davidson
	Regulatory Project Manager		Sr. Regulatory Coordinator
	Food and Drug Administration		
	Rockville, MD 20857-1706		
Phone:	301-827-4236		
Fax:	301-827-4267	Phone:	610-902-3719
		Fax:	610-964-5972

EMARKS:

☐ Urgent ☒ For your review ☐ Reply ASAP ☐ Please comment

DA No. 20-527/S-017

[redacted] (conjugated estrogens/medroxyprogesterone acetate tablets)

emphase® (conjugated estrogens/medroxyprogesterone acetate tablets)

ear Ms. Moore,

e following pages are additional minor changes to the labeling submitted by fax yesterday. I would like to draw ur attention to the first page that contains a substantial change in the section entitled "Who should not take empro or Premphase?"

ease call if you have any questions. Thank you.

Cynthia

Number of Pages Redacted 15

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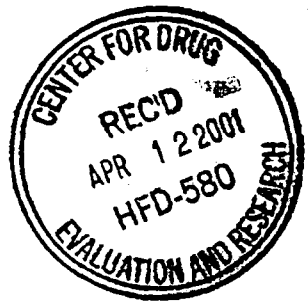
Draft Labeling
(not releasable

ORIGINAL

April 11, 2001



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

NDA SUPP AMEND

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) and PREMPHASE (conjugated estrogens / medroxyprogesterone acetate tablets) submitted to DRUDP on June 15, 2000. Reference also is made to the Agency's Discipline Review Letter faxed to Ms. Jennifer Norman (Wyeth-Ayerst) on April 4, 2001. Further reference is made to the telephone conferences with the Agency of April 5, 6, 9, and 10 regarding the MPA stability and dissolution specification.

The purpose of this submission is to amend the supplemental application S-017 in response to the Agency's comments of April 4, 2001. The revised NDA pages for sections 4.1.4.6.1 (specifications) and 4.1.4.7.3 (specifications as part of stability protocol) are also included. Wyeth-Ayerst, herein, submits responses to the following comments from the Agency:

1. Conjugated estrogens (CE) *in vitro* dissolution specifications (acceptance criteria) for the drug product.

2. Medroxyprogesterone acetate (MPA) *in vitro* dissolution specifications (method and acceptance criteria) for the drug product. As per Agency's request of April 10, 2001, a brief description of the [redacted]™ is also included.

3. Qualification of [redacted] as a supplier of [redacted]

Please note that the Agency's comments are noted in bold type, immediately followed by the Wyeth-Ayerst response.

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

P.O. BOX 42528, PHILADELPHIA, PA 19101 • (610) 688-4400

TH-346D

If you have any questions regarding this submission, please contact the undersigned at (610) 902-3743 or Dr. Joseph Sonk at (610) 902-3740.

Sincerely,

WYETH-AYERST LABORATORIES

Nirdosh Jagota, Ph.D.
Director
Worldwide Regulatory Affairs

Attachments

Desk Copy: Ms. Diane Moore
Dr. David Lin

U:\Premarin\02527 S017 FDA amend 041101 2.doc

WYETH-AYERST RESEARCH

BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

ORIGINAL

April 10, 2001

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

VIA FAX

SUPPL NEW CORRESPOND

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

Sup) 017-NC

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 letter of April 4, 2001 which requested, among other issues, the removal of the line between the trademark and the established name on the container, pouch, and carton labels. On April 9th, I discussed this issue with Ms. Moore and noted that although there are examples of competitors employing such a line, it is our intention to comply with FDA's direction for removal. We ask that FDA allow use of the line for launch purposes after which the line will be removed as directed. Enclosed is a graphic example of the proposed carton with the line. This was faxed to Ms. Moore on April 9th for the Division's review and approval.

I will call Ms. Moore today to obtain the Division's decision.

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

Sincerely,

WYETH-AYERST LABORATORIES

C H Davidson for J Sonk

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

Desk copies: DRUDP: Ms. Diane Moore, Project Manager; Dr. David Lin

JSS:beh

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS

Number of Pages Redacted 1

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WYETH-AYERST RESEARCH

) BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Ho

WORLDWIDE REGULATORY AFFAIRS

April 3, 2001

ORIGINAL

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

Noted 4/17/01

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

SC 2-017 - AIA

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.

Further reference is made to a teleconference requested by FDA and held on Friday, March 30, 2001 with Ms. Diane Moore, Dr. Theresa Van Der Vlugt, Dr. Shelley Slaughter, and Dr. Joseph Sonk, Ms. Cynthia Davidson and Ms. Jennifer Norman of Wyeth-Ayerst, regarding the status of the Medical Review of the CE/MPA Low Dose submission (NDA No. 20-527/S-017).

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

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

Desk Copy: Ms. Diane Moore

JDN:lad\809

WYETH-AYERST RESEARCH

ORIGINAL

BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of Wyeth-Ayerst Laboratories

WORLDWIDE REGULATORY AFFAIRS

March 29, 2001

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

NDA SUPP AMEND
BC

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.

Further reference is made to a verbal communication on March 6, 2001 with Dr. Nirdosh Jagota of Wyeth-Ayerst and Ms. Diane Moore and Dr. David Lin regarding the provision of updated stability data for ——— Premarin/MPA (0.45/1.5, 0.3/1.5) products to support 24 months expiry dating. Agreement was reached to provide the 24 months stability data for ——— Premarin/MPA as soon as possible taking into account the primary user fee date of April 15, 2001.

Enclosed in Volumes 1 and 2 as amendments to NDA 20-527/S-017 is the following reports:

1. RPT-39154: Report of Twenty-four Months Stability Data for Premarin/MPA 0.3/1.5mg Tablets in HDPE Bottles, EZ-Dial Packs and PVC Blisters.

   Summarized in this report are up to twenty-four months of 25°C/60%RH, twelve months of 30°C/60%RH, and six months of 40°/75% RH stability data collected from three batches of Premarin/MPA 0.3/1.5mg tablets.

   Based on the satisfactory twenty-four months stability data at 25°C/60%RH, and twelve months data at 30°C/60%RH conditions presented in this report and the attached statistical analysis (SRN01-018), an expiration dating period of at least ~ months at controlled room temperature (25°C-25°C) is supported. However, based on available real time data, an expiration dating of 24 months at controlled room temperature (25°C-

25°C) is proposed for Premarin/MPA 0.3/1.5mg tablets in HDPE bottles with CR caps, EZ-Dial Packs in foil pouch with patient package inserts, and in PVC blisters.

2. RPT-39157: Report of Twenty-four Months Stability Data for Premarin/MPA 0.45/1.5mg Tablets in HDPE Bottles, EZ-Dial Packs and PVC Blisters.

   Summarized in this report are up to twenty-four months of 25°C/60%RH, twelve months of 30°C/60%RH, and six months of 40°/75% RH stability data collected from three batches of Premarin/MPA 0.45/1.5mg tablets.

   Based on the satisfactory twenty-four months stability data at 25°C/60%RH, and twelve months data at 30°C/60%RH conditions presented in this report and the attached statistical analysis (SRN01-019), an expiration dating period of at least ——— at controlled room temperature (25°C-25°C) is supported. However, based on available real time data, an expiration dating of 24 months at controlled room temperature (25°C-25°C) is proposed for Premarin/MPA 0.45/1.5mg tablets in HDPE bottles with CR caps, EZ-Dial Packs in foil pouch with patient package inserts, and in PVC blisters.

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

Desk Copy: Ms. Diane Moore
Dr. David Lin

JDN:lad\807

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

WYETH-AYERST RESEARCH

WORLDWIDE REGULATORY AFFAIRS

March 29, 2001

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

ORIGINAL

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.

Further reference is made to Protocol 0713D2-309-US. *A Prospective, Double Blind, Randomized Study of the Safety and Efficacy of Lower Doses of Premarin and Medroxyprogesterone Acetate in Postmenopausal Women: Interim Report (GMR-38605).*

On March 26, 2001, I contacted Ms. Diane Moore to inform her of additional database findings from Protocol 0713D2-309-US that were obtained after the database was locked (December 23, 1999) for the 1-Year Interim Report (GMR-38605) and therefore not previously submitted as part of NDA No. 20-527/S-017. The purpose of my call was to inform her of this information and seek advice on the appropriate timing for submission of this information to the Agency as an amendment to the sNDA. I put this into the context of the upcoming primary user fee date of April 15, 2001. I informed Ms. Moore that, (1) the new findings are the result of information from quality assurance reviews, routine data cleanup activities resulting from these reviews, site visits by resolution of queries issued by the Clinical Data Management department, and (2) the findings have been carefully evaluated and do not change the safety and efficacy conclusions of Protocol 0713D2-309 (The HOPE Study) YEAR-1, nor do they significantly alter the labeling.

Ms. Moore confirmed with the Medical Officer, Dr. Van Der Vlugt, that this information should be submitted to the Agency as an amendment to NDA 20-527/S-017 as soon as possible as the submission is currently under active review.

The enclosed report (Volume 1) entitled:

Women's HOPE Interim sNDAs (Protocol 0713D2-309-US, formerly Prot. 0713B0309-US) Data Findings Post-Database Cutoff,

is being submitted as an amendment to NDA No. 20-527/S-017.

NDA No. 20-527/S-017 submitted on June 15, 2000, provided final data for the basic study patients as an Interim Report for study 0713D2-309-US. The enclosed report provides additional information, which was obtained after the database was locked (December 29, 1999) for the 1-Year Interim Report (GMR-38605). A summary of the findings post-database cutoff is provided in Table 1 of this report. As a result of these findings, Table 4 – treatment emergent adverse events - of the proposed labeling submitted with NDA 20-527/S-017 has been revised accordingly and is provided as Table 2 in this report. Details of all findings for each type of data from year 1 are included in the enclosed report under Supportive Tables.

This new information is being submitted for completeness and to ensure that the Division has all of the findings from Year 1 of study 0713D2-309-US (The HOPE Study) even those findings which became available after the database was locked on December 23, 1999. The additional findings provided in this submission are data from the basic study patients as well as the Year-1 data from patients who continued in the Year-2 osteoporosis and metabolic substudy.

These new findings are not the result of a detailed new analysis of previously submitted data and we do not consider it to be a major amendment to the sNDA as defined in CFR 314.60, Amendments to an unapproved application.

It should be noted that the database for study 0713D2-309-US has been corrected based on these additional findings for the substudy patients and will be included in the final report to be submitted as part of an sNDA scheduled for later this year.

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

REVIEWS COMPLETED

CSO ☐ MEMO

CSO DATE

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

Desk Copy: Ms. Diane Moore

JDN:lad\806

WYETH-AYERST RESEARCH

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

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

NDA SUPP AMEND ORIGINAL

March 23, 2001

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

CENTER FOR DRUG EVALUATION AND RESEARCH HFD-580

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.

Further reference is made to a request from Dr. David Lin on March 20, 2001 for authorization letters to reference the Drug Master Files submitted by the [redacted] used in the packaging of CE/MPA Low Dose in bottles.

In response to this request, the following DMF authorization letters are being submitted as an amendment to NDA No. 20-527/S-017:

[redacted]

[redacted]

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

Desk Copy: Ms. Diane Moore
Dr. David Lin

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

LTH-1019

WYETH-AYERST RESEARCH

PO BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

ORIGINAL

March 23, 2001

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

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

NDA SUPP AMEND

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.

Further reference is made to a request from Ms. Diane Moore on March 20, 2001 for specific patient information from the Women's HOPE Study (Protocol 0713D2-309-US) pertaining to mammogram results, breast cancer, HRT use history and urogenital history as follows:

1. Screening mammogram results for patients: 30934-0230, 30934-0047, 30946-0088, 30902-0022, 30953-0071.
2. Confirmation of a left breast cancer and pathology diagnosis for patient #30934-0230.
3. Results of cycle 7 mammogram for patient #30934-0047.
4. All pertinent urogenital history including years and type of HRT use prior to the Women's HOPE Study for patients: 30934-0230, 30934-0047, 30946-0088, 30902-0022, 30953-0071, 30929-0038, and 30908-0023.

Regarding the request for mammogram results and urogenital /HRT use history for patient 30934-0047, we believe there to be a discrepancy in this patient number as 30934-0047 discontinued the study during Cycle 3. Patient 30939-0047 was diagnosed with breast cancer during the study, as were the other 4 patients in Item #1. Therefore, information as requested for 30934-0047 is provided for 30939-0047.

REVIEWS COMPLETED

CSO ACTION:
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The following patient information is enclosed as Attachments 1 – 7:

30934-0230 – Attachment 1
- Screening (7/22/98) and Cycle 13 (8/18/99) mammogram results
- Prior Medication Record – No prior HRT use listed
- Pathology Reports (10/23/99, 11/12/99)
- Preoperative History and Physical (11/12/99)
- Operative Report (11/12/99)
- History CRF

30939-0047 - Attachment 2
- Screening mammogram (12/12/96)
- Results of clinical examination (6/10/97)
- Surgical Consultation (7/2/97) for breast evaluation performed on 6/24/97
- Right breast mammogram result (7/9/97)
- Prior Medication Record – No prior HRT use listed
- History CRF
- Note: There is no Cycle 7 bilateral mammogram

30946-0088 – Attachment 3
- Screening mammogram (7/17/97) and 6 month mammogram (1/24/98)
- Prior Medication Record – No prior HRT use listed
- History CRF

30902-0022 – Attachment 4
- Screening mammogram (10/22/96)
- Prior Medication Record – No prior HRT use listed
- History CRF

30953-0071 – Attachment 5
- Screening mammogram (6/23/98)
- Prior Medication Record – No prior HRT use listed
- History CRF

30929-0038 – Attachment 6
- History and Prior Medication CRF – Prior HRT use – Premarin and Provera

30908-0023 – Attachment 7
- History and Prior Medication CRF – No prior HRT use

The medical history, prior treatment record, screening mammography report, and study termination report are included for patient 30934-0047 as Attachment 8 for your reference.

Lastly, Ms. Moore had requested that we provide any additional experience we have that was not in the sNDA 20-527/S-017, which indicates that regimens containing 0.3mg conjugated estrogens (CE) may not provide optimal relief of vasomotor symptoms. With the exception of patient responses to an unvalidated quality of life questionnaire, all data on CE 0.3mg and CE 0.3mg/1.5mg MPA were included in the sNDA.

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

Desk Copy: Ms. Diane Moore

JDN:lad\805

WYETH-AYERST RESEARCH

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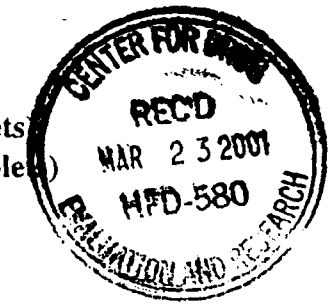
Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

ORIGINAL

March 22, 2001



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

NDA SUPP AMEND

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

SE2017 (BS)

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.

Further reference is made to a request from Ms. Diane Moore on March 15, 2001 for an additional analysis of vaginal maturation index (VMI) data from the Women's HOPE Study (Protocol 0713D2 – 309-US).

Ms. Moore requested that the VMI data be presented in a table with "Maturation Results" as part of the title. Each dose group from HOPE (A-H) should be listed across the top of the table with Parabasal Cells %, Intermediate Cells% , Superficial Cells% on the left side. For each dose group across the top, baseline mean +/- std error for cycles 6 and 13 should be provided with mean change +/- std error as the last column.

After discussing the request with our statistician, Dr. Northington, I contacted Ms. Moore on March 15, 2001 to confirm specifics of the request including changes we proposed regarding format of the table. Ms. Moore confirmed the following on March 19, 2001:

- Mean data are requested, not median data.
- Last observation carried forward (LOCF) should be included.
- It is acceptable to change the suggested format of the table to list the dosage groups on left side, columns to include baseline mean and mean change from baseline at cycles 6 and 13.

Enclosed for submission as an amendment to NDA No. 20-527/S-017 is the following table:

SUMMARY OF MATURATION INDEX RESULTS – MEAN VALUES AND COMPARISONS BETWEEN ACTIVE TREATMENT GROUPS AND THE PLACEBO GROUP BY CYCLE
LOCF

All patients who had data at baseline and at least one post-baseline visit are included. A last observation carried forward approach was used. In cases where a patient had data at baseline and cycle 13 only, the baseline value was carried forward to cycle 6.

All of the active groups showed significantly greater increases in superficial and intermediate cells than placebo and significantly greater decreases in parabasal cells than placebo.

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

JDN:lad\804

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

WYETH-AYERST RESEARCH

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

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

ORIGINAL

March 15, 2001

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

NDA SUPP AMEND
SE2 017 (MR)

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

See 4/4/01 IR letter DM

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 the FDA on June 15, 2000.

Further reference is made to Wyeth-Ayerst's tradename proposal, —, for the low dose CE/MPA products (0.45mg/1.5mg, 0.3mg/1.5mg) submitted on November 10, 2000 and additional supportive information submitted on February 6, 2001 to DRUDP.

Earlier this year, Ms. Moore, Project Manager of DRDUP, had noted that preliminary feedback from OPDRA was not favorable for the — tradename. During the first week of March 2001, Wyeth-Ayerst was informed that the Agency is not likely to accept Wyeth-Ayerst's rationale for the — tradename, and that this —

The purpose of this submission is to request a meeting (within 2 weeks if possible) with the appropriate personnel from DRUDP, OPDRA and other CDER personnel as appropriate, to (1) understand the rationale for the Agency's position on the — tradename; (2) present new data in support of —, emphasizing the importance of the tradename as a driver to prescribing lower doses and (3) understand how Wyeth-Ayerst can provide supportive information to all interested CDER disciplines during deliberation on this issue.

As per the Manual of Policies and Procedures for requesting formal meetings between CDER and CDER's external constituents, the following is provided:

Meeting Purpose:
The main purpose is to present additional market research data and rationale in support of a separate tradename(s) for CE/MPA low dose products (NDA 20-527/S-017).

Objectives:
To understand the Agency's process and concerns for approving a new tradename for low dose CE/MPA products.
To obtain concurrence with DRUDP, OPDRA and other CDER personnel as appropriate on the importance of a new tradename, — for the low dose CE/MPA products.
To review new data from Wyeth-Ayerst in support of the tradename —.

Proposed Agenda:
1) Introduction – 5 minutes – Ms. Diane Moore/Dr. Joseph Sonk
2) Wyeth-Ayerst presentation – 15 minutes
3) Discussion – 40 minutes

Proposed Wyeth-Ayerst Meeting Attendees:

Dr. Michael Dey, President, Women's Healthcare Business/designee
Ms. Heidi Hunter, Vice President, Women's Healthcare Marketing
Ms. Mary Beth Sandin, Executive Director, Women's Healthcare Marketing
Dr. James Pickar, Assistant Vice President, Clinical Research and Development
Dr. Bruce Burlington, Senior Vice President, Worldwide Regulatory Affairs & Compliance/designee
Dr. Joseph Sonk, Assistant Vice President, Women's Healthcare, Worldwide Regulatory Affairs
Expert Consultant on Medication Errors/Nomenclature

Requested FDA Attendees:

The appropriate Agency personnel from DRUDP, OPDRA, and other CDER personnel as appropriate.

Supporting Documentation:
Supporting documentation will be provided within 1 week of receipt of this request.

Due to the time constraints with the approaching primary user fee date of April 15, 2001, we hereby request that the meeting be held within the next 2 weeks. Thank you in advance for your consideration in accepting our meeting proposal.

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

JDN:lad\801

WYETH-AYERST RESEARCH

BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

ORIGINAL

March 15, 2001

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

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

NDA SUPP AMEND

SE2017 (BM)

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.

Further reference is made to a request from Ms. Diane Moore on March 9, 2001 for new analyses of vasomotor symptom data from Protocol 0713D2-309-US. The previous analyses of VMS data submitted to DRUDP on March 8, 2001, were not exactly what the Division had expected in response to the request of February 14, 2001. As clarified by Drs. Van Der Vlugt and Kammerman and Ms. Moore in a teleconference with Dr. R. Northington and Ms. Norman of Wyeth-Ayerst on March 9, 2001, analyses for the subset of patients who met the criteria of 7-8 flushes per day or 50 per week at baseline with LOCF are requested for weeks 4, 8, and 12. In addition, the new tables enclosed as Attachment I provide baseline means and mean changes as requested.

Attachment I

- Table 1: Summary Tabulation of the Number of Hot Flushes-Mean Values and Comparisons Between the Active Treatment Groups and the Placebo Group by Week, Patients with at Least 7 Moderate to Severe Flushes Per Day or at Least 50 Per Week at Baseline, LOCF
- Table 2: Summary Tabulation of the Severity of Hot Flushes-Mean Values and Comparisons Between the Active Treatment Groups and the Placebo Group by Week, Patients with at Least 7 Moderate to Severe Flushes Per Day or at Least 50 Per Week at Baseline, LOCF

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

JDN:lad\800

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ATTACHMENT I

TABLE 1: SUMMARY TABULATION OF THE NUMBER OF HOT FLUSHES - MEAN VALUES AND COMPARISONS BETWEEN THE ACTIVE TREATMENT GROUPS AND THE PLACEBO GROUP BY WEEK PATIENTS WITH AT LEAST 7 MODERATE TO SEVERE FLUSHES PER DAY OR AT LEAST 50 PER WEEK AT BASELINE, LOCF

Treatment[a]		---------- No. of Hot Flushes/Day --------			
Time Period (week)	No. of Patients	Baseline Mean ± SD	Mean Change ± SE	Adjusted Mean ± SE[b]	p-Values vs. Placebo[c]
Group A 0.625					
4	27	12.29 ± 3.89	-10.34 ± 0.91	1.96 ± 0.73	<0.001
8	27	12.29 ± 3.89	-11.32 ± 0.94	0.98 ± 0.65	<0.001
12	27	12.29 ± 3.89	-11.54 ± 0.89	0.75 ± 0.60	<0.001
Group B 0.625/2.5					
4	34	11.98 ± 3.54	-8.78 ± 0.81	3.38 ± 0.66	<0.001
8	34	11.98 ± 3.54	-10.51± 0.84	1.52 ± 0.61	<0.001
12	34	11.98 ± 3.54	-10.82 ± 0.79	1.21 ± 0.54	<0.001
Group C 0.45					
4	32	12.25 ± 5.04	-7.21 ± 0.84	5.07 ± 0.67	<0.001
8	32	12.25 ± 5.04	-9.41 ± 0.87	2.84 ± 0.63	<0.001
12	32	12.25 ± 5.04	-9.93 ± 0.82	2.33 ± 0.56	<0.001
Group D 0.45/2.5					
4	28	12.73 ± 3.33	-10.03 ± 0.89	2.57 ± 0.72	<0.001
8	28	12.73 ± 3.33	-11.31 ± 0.93	1.36 ± 0.67	<0.001
12	28	12.73 ± 3.33	-11.51 ± 0.87	1.16 ± 0.59	<0.001
Group E 0.45/1.5					
4	29	12.61 ± 4.29	-8.98 ± 0.88	3.54 ± 0.71	<0.001
8	29	12.61 ± 4.29	-10.39 ± 0.91	2.17 ± 0.66	<0.001
12	29	12.61 ± 4.29	-10.92 ± 0.86	1.64 ± 0.58	<0.001
Group F 0.3					
4	30	13.77 ± 4.78	-9.12 ± 0.86	4.19 ± 0.70	<0.001
8	30	13.77 ± 4.78	-10.76 ± 0.89	2.77 ± 0.65	<0.001
12	30	13.77 ± 4.78	-11.25 ± 0.84	2.29 ± 0.58	<0.001
Group G 0.3/1.5					
4	33	11.30 ± 3.13	-7.60± 0-.82	4.01 ± 0.67	<0.001
8	33	11.30 ± 3.13	-8.84± 0.85	2.63± 0.62	<0.001
12	33	11.30 ± 3.13	-10.00 ± 0.80	1.47 ± 0.55	<0.001
Group H Placebo					
4	28	11.69 ± 3.87	-3.80 ± 0.89	8.09 ± 0.72	-
8	28	11.69 ± 3.87	-4.86 ± 0.93	6.93 ± 0.67	-
12	28	11.69 ± 3.87	-5.98 ± 0.87	5.81 ± 0.59	-

a Identified by dosage (mg) of CE or CE/MPA.
b Standard errors based on assumption of equal variances.
c: Based on analysis of covariance with treatment as factor and baseline as covariate.

TABLE 2: SUMMARY TABULATION OF THE SEVERITY OF HOT FLUSHES – MEAN VALUES AND COMPARISONS BETWEEN THE ACTIVE TREATMENT GROUPS AND THE PLACEBO GROUP BY WEEK PATIENTS WITH AT LEAST 7 MODERATE TO SEVERE FLUSHES PER DAY OR AT LEAST 50 PER WEEK AT BASELINE, LOCF

Treatment[a]		-------- Hot Flushes, Mean Severity -------			
Time Period (Week)	No. of Patients	Baseline Mean ± SD	Mean Change ± SE	Adjusted Mean ± SE[b]	p-Values vs. Placebo[c]
Group A 0.625					
4	27	2.26 ± 0.34	-1.38 ± 0.16	0.90 ± 0.16	<0.001
8	27	2.26 ± 0.34	-1.77 ± 0.16	0.50 ± 0.16	<0.001
12	27	2.26 ± 0.34	-1.90 ± 0.17	0.37 ± 0.16	<0.001
Group B 0.625/2.5					
4	34	2.33 ± 0.33	-1.23 ± 0.14	1.07 ± 0.14	<0.001
8	34	2.33 ± 0.33	-1.77 ± 0.15	0.54 ± 0.14	<0.001
12	34	2.33 ± 0.33	-1.79 ± 0.15	0.52 ± 0.14	<0.001
Group C 0.45					
4	32	2.33 ± 0.39	-0.97 ± 0.14	1.34 ± 0.14	<0.001
8	32	2.33 ± 0.39	-1.33 ± 0.15	0.98 ± 0.15	<0.001
12	32	2.33 ± 0.39	-1.47 ± 0.15	0.85 ± 0.15	<0.001
Group D 0.45/2.5					
4	28	2.29 ± 0.33	-1.30 ± 0.15	0.99 ± 0.15	<0.001
8	28	2.29 ± 0.33	-1.81 ± 0.16	0.48 ± 0.16	<0.001
12	28	2.20 ± 0.33	-1.84 ± 0.16	0.45 ± 0.16	<0.001
Group E 0.45/1.5					
4	29	2.17 ± 0.38	-0.99 ± 0.15	1.27 ± 0.15	<0.001
8	29	2.17 ± 0.38	-1.40 ± 0.16	0.84 ± 0.16	<0.001
12	29	2.17 ± 0.38	-1.54 ± 0.16	0.67 ± 0.16	<0.001
Group F 0.3					
4	30	2.38 ± 0.37	-0.92 ± 0.15	1.40 ± 0.15	<0.001
8	30	2.38 ± 0.37	-1.35 ± 0.16	0.98 ± 0.15	<0.001
12	30	2.38 ± 0.37	-1.27 ± 0.16	1.09 ± 0.15	<0.001
Group G 0.3/1.5					
4	33	2.24 ± 0.31	-0.79 ± 0.14	1.48 ± 0.14	<0.001
8	33	2.24 ± 0.31	-1.34 ± 0.15	0.93 ± 0.15	<0.001
12	33	2.24 ± 0.31	-1.67 ± 0.15	0.58 ± 0.15	<0.001
Group H Placebo					
4	28	2.37 ± 0.34	-0.29 ± 0.15	2.03 ± 0.15	-
8	28	2.37 ± 0.34	-0.57 ± 0.16	1.76 ± 0.16	-
12	28	2.37 ± 0.34	-0.72 ± 0.16	1.62 ± 0.16	-

a Identified by dosage (mg) of CE or CE/MPA.
b Standard errors based on assumption of equal variances.
c: Based on analysis of covariance with treatment as factor and baseline as covariate.

WYETH-AYERST RESEARCH

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

Division of American Home Products Corporation

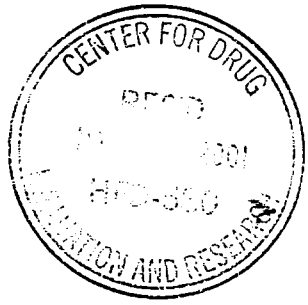
WORLDWIDE REGULATORY AFFAIRS

ORIGINAL

March 13, 2001

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

NDA SUPP AMEND



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.

Further reference is made to a request by Dr. David Lin on February 7, 2001 to Dr. J. Sonk for additional stability data on batches of Low Dose CE/MPA (12 month data were submitted with NDA 20-527/017) and any reprocessing documentation of manufactured material for Low Dose CE/MPA. On March 6, 2001, Dr. Nirdosh Jagota of Wyeth-Ayerst contacted Ms. Diane Moore and Dr. David Lin requesting an extension of the March 9, 2001 deadline for receipt of the additional stability data (18 month). An extension to March 13, 2001 was granted for receipt of the 18 month stability data with the commitment by Wyeth-Ayerst to provide 24 month stability data as soon as possible to allow for at least one week review by FDA prior to the primary user fee date of April 15, 2001.

The following 18 month stability reports are being submitted as an amendment to NDA 20,527/S-017 :

Volume 1

- RPT-39154: Report of Eighteen Months Stability Data for Premarin/MPA 0.3mg/1.5mg Tablets in HDPE Bottles, EZ-Dial Packs and PVC Blisters and statistical evaluation (SRN01-011).

The report includes 18 months stability data on CE/MPA 0.3mg/1.5mg stored at 25°C/60%RH, 12 months data at 30°C/60%RH, and 6 months data at 40°C/75%RH. Based on satisfactory 18 months stability data at 25°C/60%RH and 12 months data at 30°C/60%RH (blisters) a tentative expiration dating period of 24 months at controlled room temperature is proposed for Premarin/MPA 0.3mg/1.5mg tablets in HDPE bottles, PVC blisters and EZ-Dial Packs in foil pouches.

Volume 2

- RPT-39157: Report of Eighteen Months Stability Data for Premarin/MPA 0.45mg/1.5mg Tablets in HDPE Bottles, EZ-Dial Packs and PVC Blisters.

  The report includes 18 months stability data on CE/MPA 0.45mg/1.5mg stored at 25°C/60%RH, 12 months data at 30°C/60%RH, and 6 months data at 40°C/75%RH. Based on satisfactory 18 months stability data at 25°C/60%RH and 12 months data at 30°C/60%RH a tentative expiration dating period of 24 months at controlled room temperature is proposed for Premarin/MPA 0.45mg/1.5mg tablets in HDPE bottles, PVC blisters and EZ-Dial Packs in foil pouches.

In response to Dr. Lin's request for reprocessing steps included in the manufacturing directions or batch records, we confirm that there are no reprocessing steps for the low dose CE/MPA products.

On March 9, 2001, Dr. Lin had requested of copy of the letter of authorization from for the components of the EZ-Dial pack. Enclosed are the July 13, 2000 letters of authorization to reference and the letter from , describing the amendments to

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Desk Copy: Dr. David Lin

WYETH-AYERST RESEARCH

PO BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

ORIGINAL

March 7, 2001

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

NDA SUPP AMEND
Seq-017 BM

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 on June 15, 2000.

On February 14, 2001, Ms. Diane Moore had verbally requested additional analyses of VMS (vasomotor symptom) data and VMI (vaginal maturation index) data from Protocol 0713D2-309-US using the Intent to Treat Population (ITT) by week, last observation carried forward (LOCF). I had requested further clarification on the request regarding VMI data since, as per Protocol 0713D2-309-US, VMI analyses were conducted for cycles 6 and 13 only. On February 28, 2001, Ms. Moore confirmed that additional analyses of VMI were not needed at this time. In response to the request for additional analyses of VMS data, enclosed as Attachment I are the following data presented in tabular format preceded by a one page summary:

- Table 1: Summary tabulation of the number of hot flushes-adjusted means and comparisons between the active treatment groups and the placebo group by week – ITT population, LOCF

- Table 2: Summary tabulation of the number of hot flushes-adjusted means and comparisons between the active treatment groups and the placebo group by week – ITT population, LOCF

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

JDN:lad\794

APPEARS THIS WAY
ON ORIGINAL

WYETH-AYERST RESEARCH

PO BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

ORIGINAL

February 28, 2001

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

NDA SUPP AMEND

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 the FDA on June 15, 2000.

In response to Ms. Diane Moore's request of February 28, 2001 for a copy of the CPMP Points to Consider on Hormone Replacement Therapy, please find enclosed a copy of the following document:

Committee for Proprietary Medicinal Products (CPMP)
Points to Consider on Hormone Replacement Therapy
CPMP/EWP/021/97
November 19, 1997

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

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

JDN:lad\791

LTH-1019

WYETH-AYERST RESEARCH

PO BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

ORIGINAL

February 28, 2001

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

NDA SUPP AMEND
S48-017-B17

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 the FDA on June 15, 2000.

In response to Dr. Ameeta Parekh and Dr. John Lau's request via telephone on February 13, 2001 for complete in-vitro dissolution profiles for clinical batches and registration batches of the strengths of CE/MPA proposed for marketing (0.45 mg/1.5mg, [redacted] referenced in sNDA 20-527/S-017, dissolution profiles on the following batches are provided (Attachment I) in tabular format, as well as brief summary of the data, as committed to by February 28, 2001:

Table No.	Strength	Formulation	Batch No.	Date of Manufacture
1	[redacted]			
2				
3				
4				
5				
6	0.45/1.5 mg	Clinical	3TEM	November 1993
7	0.45/1.5 mg	Clinical	1997B0089	July 1997
8	0.45/1.5 mg	Market	R982756	July 1998
9	0.45/1.5 mg	Market	R982757	July 1998
10	0.45/1.5 mg	Market	R982758	July 1998

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS

LT4-1019

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

JDN:lad\790

Desk Copy: Dr. Ameeta Parekh, Dr. John Lau
Dr. David Lin

APPEARS THIS WAY
ON ORIGINAL

WYETH-AYERST RESEARCH

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

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

DUPLICATE

February 23, 2001

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

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

SC2-017-SC

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 on June 15, 2000.

In response to Dr. David Lin's request via telephone on February 8, 2001 for individual dissolution data on specific clinical batches of CE/MPA 0.45mg/1.5mg and [redacted] enclosed are individual dissolution values presented in tabular format (Attachment I) for clinical batches 3TEM (0.45mg/1.5mg) and 3THN [redacted] utilized in the following studies:

Protocol 0713D2-119-US (GMR 32506)
Protocol 0713D2-120-US (GMR 32507)
Protocol 0713D2-309-US (GMR 38605)

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

Desk Copy: Dr. David Lin

LTH-10[illegible]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Wyeth-Ayerst Laboratories	February 23, 2001
TELEPHONE NO. (Include Area Code) (610) 902-3749	FACSIMILE (FAX) Number *(Include Area Code)* (610) 964-5969
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): P.O. Box 8299 Philadelphia, PA 19101	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-527/S-017

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
Conjugated Estrogens/Medroxyprogesterone Acetate Tablets	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)	CODE NAME (*If any*)

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	0.45/1.5, 0.3/1.5	Oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of vasomotor sypmtoms associated with menopause. Treatment of vulvar and vaginal atrophy.

APPLICATION INFORMATION

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

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

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

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

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ PRIOR APPROVAL (PA)

REASON FOR SUBMISSION
Response to request from FDA for dissolution data on clinical batches.

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

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

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

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

	This application contains the following items: *(Check all that apply)*
☐	1. Index
☐	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
☐	8. Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2)
☐	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
☐	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
☐	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
☐	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.5 (k) (3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER (Specify) Response to FDA request for dissolution data on clinical batches.

CERTIFICATION

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

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

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

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

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

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Jennifer D. Norman	Jennifer D. Norman, Associate Director	2/23/01

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
P.O Box 8299, Philadelphia,PA 19101	(610) 902-3749

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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

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

Attachment I

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 2

❖❖❖

Confidential,
Commercial Information

WYETH-AYERST RESEARCH

• PHILADELPHIA, PA 19101-8299 Division of American Home Products Corporation

DE REGULATORY AFFAIRS

ORIGINAL

February 7, 2001

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

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

NDA SUPP AMEND
SC 2-017 DC

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 on June 15, 2000.

In response to Ms. Diane Moore's and Mr. David Lin's request on January 26, 2001 for samples of CE 0.45mg/MPA 1.5mg and CE 0.3mg/MPA 1.5mg finished product and packaging samples, the following are enclosed:

- CE 0.45mg/MPA 1.5 mg (Batch# R009672) - 10 tablets packaged in bottles; CE 0.3 mg/MPA 1.5 mg (Batch# R009676) - 10 tablets packaged in bottles.
- EZ Dial – 3 samples of empty pack for CE 0.45 mg/MPA 1.5 mg. Samples of CE 0.3 mg/ MPA 1.5 mg are not yet available; however, packaging components for EZ Dial will be identical to packaging components for EZ Dial for CE 0.45mg/MPA 1.5mg.
- Blister packs – 3 samples of blister packs (physician samples) of marketed PREMPRO (0.625 mg/ 2.5mg) are enclosed. Blisters of CE 0.45 mg/ MPA 1.5 mg and CE 0.3 mg/ MPA 1.5 mg for physician samples are not yet available; however the packaging components for blisters for CE 0.45 mg/MPA 1.5mg and CE 0.3 mg/MPA 1.5 mg will be identical to that of the marketed product PREMPRO.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

JDN:lad\782

Desk Copy: Mr. David Lin

APPEARS THIS WAY
ON ORIGINAL

WYETH-AYERST RESEARCH

O. BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

ORLDWIDE REGULATORY AFFAIRS

ORIGINAL

February 6, 2001

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

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

SUPPL NEW CORRESP

SNC-017

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 on June 15, 2000.

Further reference is made to our previous submission dated November 10, 2000 to NDA No. 20-527/S-017 regarding Wyeth-Ayerst's proposal for a separate tradename, —— for CE/MPA Low Dose.

Our proposal, in support of a new tradename, —— for CE/MPA Low Dose (CE 0.45 mg/ MPA 1.5 mg, CE 0.3 mg/ MPA 1.5 mg), has been submitted in an effort to reduce confusion that currently exists among physicians when prescribing PREMPRO; that is, inconsistency in designating the dosage of MPA when prescribing PREMPRO. PREMPRO dosages differ in the potency of MPA only; the potency of CE is the same (CE 0.625 mg/ 5 mg MPA, CE 0.625 mg/ 2.5 mg MPA. The addition of two new dosages of CE/MPA to the marketplace will likely cause further confusion particularly because the new dosages differ in potency of CE only; the MPA potency is the same in both products.

To further support our proposal for —— as a new tradename for CE/MPA Low Dose, Wyeth-Ayerst recently conducted two quantitative surveys with physicians and pharmacists and one qualitative survey with physicians as described below:

- **Physician Survey: Fax survey with 136 OB/GYNs conducted during a three-day period in January 2001.** The physician survey found that a majority of OB/GYNs thought that branding CE/MPA Low Dose product with the PREMPRO name would be confusing to both physicians and pharmacists. A larger majority of physicians also expressed that a new name would cause less confusion in prescribing and dispensing the new product.(Attachment A)

[redacted]

- **Pharmacist Survey: Fax Survey with 111 pharmacists conducted during a one-week period in January 2001.** A large majority of pharmacists expressed that branding the CE/MPA Low Dose product as PREMPRO would cause confusion among physicians and pharmacists. Respondents also expressed that using the tradename PREMPRO for CE/MPA Low Dose 0.45/1.5 would cause more confusion in dispensing prescriptions than if the product was given its own tradename. Similar to the physician survey above, pharmacists also preferred a new tradename. (Attachment B)

- **Qualitative Research Review: Four days of interviews in four cities (Chicago, Dallas, Baltimore, Atlanta) with 40 physicians (OB/GYNS and PCPs) as part of two different research projects were conducted during November 2000 and January 2001.** Qualitative research demonstrated that a majority of physicians thought that the PREMPRO tradename would be less confusing compared to a new tradename mainly due to familiarity with the PREMPRO tradename, which would make the product easier to remember. Physicians who preferred the proposed tradename —— liked that it would preclude the necessity to remember to write dosages and consequently eliminate potential confusion and phone calls from pharmacists. In addition, these physicians commonly expressed that patients would have an easier time identifying the product they are taking when referring to their brand of HRT, thus making communication between physician and patient easier. (Attachment C)

The results of the surveys described above are enclosed as Attachment A, B, and C.

In evaluating the tradename proposal, it is requested that enclosed surveys be taken into consideration as additional evidence of the confusion that exists among physicians and pharmacists when prescribing and dispensing the appropriate dosage of PREMPRO. Introduction of two additional dosage strengths to the marketplace that differ in potency of CE and MPA compared to the marketed product PREMPRO will add to this confusion. A new tradename, —— will help physicians and pharmacists make an easy association with the Low Dose product and thereby accurately prescribe and dispense the appropriate dosage.

Based on the results from the enclosed surveys and the rationale included with our previous submission on the tradename proposal, we believe that a separate tradename will provide clarity in prescribing the appropriate dosage of CE/MPA.

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

REVIEWS COMPLETED

ACTION:
LETTER ☐ N.A.I. ☐ MEMO

INITIALS DATE

WYETH-AYERST RESEARCH

PO BOX 8299 • PHILADELPHIA, PA 19101-8299

WORLDWIDE REGULATORY AFFAIRS

Division of American Home Products Corporation

February 2, 2001

NDA No. 04-782/S-115
Premarin® (conjugated estrogens tablets, USP) **NDA SUPP AMEND**

NDA No. 20-527/S-017 SC2-017-BM
Prempro ™ (conjugated estrogens/medroxyprogesterone acetate tablets)
Premphase® (conjugated estrogens/medroxyprogesterone acetate tablets)

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

Further reference is made to the Interim Study Report (GMR 38605) for Protocol No. 713D2-309-US, *"A Prospective, Double-Blind, Randomized Study of the Safety and Efficacy of Lower Doses of Premarin and Medroxyprogesterone Acetate in Postmenopausal Women,"* (the HOPE study) included in the above submissions.

In response to Ms. Diane Moore's request by telephone on January 30, 2001, enclosed are copies of all pathology reports available from pathologists 1, 2, and 3 for the following patients who developed endometrial hyperplasia during treatment:

#30912- 0049 - Group E (CE 0.45/1.5 MPA)
#30924-0011 - Group F (CE 0.3)
#30908-0003 - Group G (CE 0.3/1.5 MPA)
#30936-0006 - Group A (CE 0.625)
#30908-0002 - Group A (CE 0.625)

For patient #30924-0011, in addition to the pathology reports, follow-up reports are provided from a consult slide review and repeat endometrial biopsy. For those patients who had a hysterectomy, surgical pathology reports are also provided.

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

JDN:lad\780

APPEARS THIS WAY
ON ORIGINAL

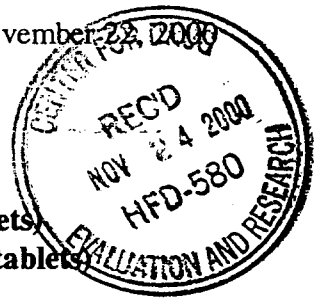
WYETH-AYERST RESEARCH

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

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

November 22, 2000



NDA No. 04-782/S-115
Premarin® (conjugated estrogens tablets, USP)

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

General Correspondence
(Financial Disclosure)

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

BM
NDA SUPP AMEND
SE2-017

Dear Dr. Allen:

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

In response to requests from Ms. Lana Pauls and Ms. Kim Calangelo for information on investigators for Protocol No. 713D2-309-US, which did not provide Financial Disclosure forms, enclosed are the following certification and disclosure documents:

- Certification: Financial Interests and Arrangements of Clinical Investigators (Form 3454).
- Disclosure: Financial Interests and Arrangements of Clinical Investigators (Form 3455).

For those investigators who have not provided Financial Disclosure forms, the following mechanisms for follow up were employed:

- Telephone calls to the investigational sites and/or universities requesting additional information on investigators with missing Financial Disclosure forms including Deans' Offices and Medical Affairs' Offices of the universities.
- Faxes were sent where the sites indicated that they might have a forwarding address or where Wyeth found a match as a result of Internet searches.
- Medical Monitor contact from previous professional associations.

- Internet searches of personnel directories from various professional organizations, e.g., ACOG, AMA, North American Menopause Society, and American Society of Reproductive Medicine.
- E-mail to site if site or Internet provided an E-mail address.

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman, Manager
Worldwide Regulatory Affairs

JDN:lad\761

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Wyeth-Ayerst Laboratories	November 22, 2000
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(610) 902-3749	(610) 964-5969
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):	**AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE**
P.O. Box 8299 Philadelphia, PA 19101	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 04-732/S-115

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)	PROPRIETARY NAME (trade name) IF ANY
Conjugated Estrogen Tablets	Premarin

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)

CODE NAME (If any)

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	0.45mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of vasomotor sypmtoms associated with menopause. Treatment of vulvar and vaginal atrophy.

APPLICATION INFORMATION

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

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

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

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

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ PRIOR APPROVAL (PA)

REASON FOR SUBMISSION
Response to request for financial disclosure information.

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

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

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

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

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

☐	1. Index
☐	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
☐	8. Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2)
☐	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
☐	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
☐	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
☐	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.5 (k) (3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☒	19. Financial Information (21 CFR Part 54)
☐	20. OTHER (Specify)

CERTIFICATION

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

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

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

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

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

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Jennifer D. Norman	Jennifer D. Norman, Manager	11/22/00

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
P.O Box 8299, Philadelphia,PA 19101	(610) 902-3749

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Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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