CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-527/S-006

CORRESPONDENCE

WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

NDA No. 20-527/S-006
Prempro™ Tablets

January 5, 1998

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Document Control Room 17B-20
Food and Drug Administration (HFD-580)
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Rarick:

Reference is made to our approved New Drug Application No. 20-527 for Prempro™ (conjugated estrogens/medroxyprogesterone acetate) tablets. Reference is also made to pending supplemental application S-006 that provides for a continuous 0.625 mg conjugated estrogens/5 mg medroxyprogesterone acetate, "Prempro" dosing regimen. Further reference is made to an amendment submitted to the Division on December 31, 1997 that provided annotated draft labeling for S-006 in response to the FDA's letter dated December 18, 1997 which provided comprehensive comments on this supplemental application.

The purpose of this communication is to provide the Agency with four copies of revised draft labeling which incorporates the annotations from the above-referenced December 31, 1997 amendment.

We trust that you will find this revised draft labeling satisfactory and will approve supplemental application S-006 at your earliest convenience. As requested, we will have the appropriate Wyeth-Ayerst personnel available for a teleconference scheduled with the Division for Tuesday, January 6, 1998 at 1:00 pm to discuss this labeling.

Should you have any questions regarding this information, please contact the undersigned at (610) 902-3740 or Mr. Robert Quinty at (610) 902-3789.

Sincerely,
WYETH-AYERST LABORATORIES

Joseph S. Sonk, Senior Director
Women's Healthcare
U.S. Regulatory Affairs

c.c.: Ms. Diane Moore, CSO, FDA
Heidi Jolson, M.D, DRUDP, FDA
Theresa Van der Vlugt, M.D., DRUDP, FDA
rhq:/soo6a2

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Wyeth-Ayerst Laboratories	1/5/98
TELEPHONE NO. *(Include Area Code)* (610) 902-3772	**FACSIMILE (FAX) Number** *(Include Area Code)* (610) 964-5972
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 19101-8299	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE P.O. Box 8299 Philadelphia, PA 19101-8299

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA No. 20-527

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	CODE NAME *(If any)*
(conjugated estrogens/medroxyprogesterone acetate	PREMPRO/PREMPHASE	

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

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	0.625/2.5mg, 0.625/5mg	oral

(PROPOSED) INDICATION(S) FOR USE:
Severe to moderate vasomotor symptoms associated with menopause and osteoporosis

APPLICATION INFORMATION

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

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

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

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

REASON FOR SUBMISSION Provide for a continuous 0.625 conjugated estrogens/5mg MPA regimen

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

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

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

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

IND NDA 20-303
NDA 04-782

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 Microbioblogy (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	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 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. 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
	Joseph S. Sonk, Senior Director	1/5/98

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

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing 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:

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

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

FORM FDA 356h (7/97)

ORIGINAL

WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corporation

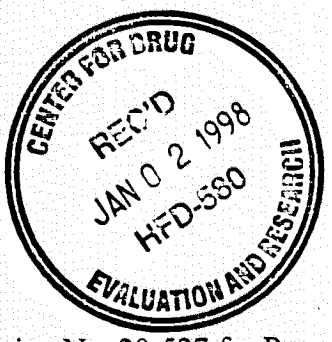
U.S. REGULATORY AFFAIRS

NDA No. 20-527/S-006
Prempro™ Tablets

NDA SUPP AMEND
SE2-006 BL

December 31, 1997

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Document Control Room 17B-20
Food and Drug Administration (HFD-580)
5600 Fishers Lane
Rockville, MD 20857



Dear Dr. Rarick:

Reference is made to our approved New Drug Application No. 20-527 for Prempro™ (conjugated estrogens/medroxyprogesterone acetate) tablets. Reference is also made to pending supplemental application S-006 that provides for a continuous 0.625 mg conjugated estrogens/5 mg medroxyprogesterone acetate, "Prempro" dosing regimen.

Further reference is made to FDA's letter dated December 18, 1997 which provided comprehensive comments on this supplemental application.

The purpose of this communication is to amend pending supplemental application S-006 in response to the Agency's above-referenced letter. Wyeth-Ayerst has agreed to incorporate all of FDA's suggestions with one exception as noted on page 2 of this letter. Noted below are our responses to FDA's requests for proposed labeling. Where cited, FDA comment page numbers refer to the clean draft as provided by the Agency in their December 18, 1997 letter which is included here with annotations. Revised draft labeling with these revisions will be submitted shortly.

Pharmacokinetics-Absorption subsection:

- FDA Comment (page 5):

  "Please provide CL/F (L/h) values for the above table."

Response:

We believe that CL/F values for conjugated estrogens can not be added to the table. As explained previously in a facsimile transmission dated December 29, 1994 from Ms. JoAnne Bissinger (Attachment 1), Wyeth-

Ayerst to Ms. Christina Kish, CSO, FDA "clearance values can not be calculated without the potency of the individual estrogens since the nominal 0.625 mg dose represents the sum of the individual conjugated estrogens."

Clinical Studies subsection (page 7, Description of Amenorrhea)

- We acknowledge the Division's suggestion to include information only from the enrolled patients when describing the cumulative incidence of amenorrhea over time. Wyeth-Ayerst proposes that this analysis be supplemented with an additional figure which summarizes cumulative amenorrhea over time for all patients having completed the study (Attachment 2). This analysis is consistent with that typically conducted for this type of endpoint. Moreover, providing both analyses to the prescriber provides a meaningful definition of the limits of the data collected. For example, reporting only the analysis of completers does not account for patients who dropped out because of bleeding, whereas describing the results from only those enrolled assumes that all patients who dropped out did so for reasons related to bleeding. The inclusion of analyses of both completers and those enrolled for both treatment regimens A and B also ensures consistency with the currently approved labeling which displays both sets of data for the Premarin 0.625mg/MPA 2.5mg regimen.

- Finally, to again ensure consistency of communication, we are now proposing that the textual summary for these figures refer to cycles 9 through 13 as detailed in the currently approved Prempro physician insert. **As noted in Attachment 2, the textual description immediately preceding the charts now states:**

  "The following two figures describe cumulative amenorrhea which is defined as amenorrhea continuing from a given cycle to the end of the study. Of women in Regimen A (n=278) and in Regimen B (n=278) who completed the study, the incidence of cumulative amenorrhea from cycle 9 through 13 was 49% and 61%, respectively. The incidence of cumulative amenorrhea for all women enrolled was 40% and 50% for Regimens A (n=340) and B (n=338), respectively."

- FDA Comment (page 7):

  "Please provide a description of the type and amount of bleeding that occurred during the study according to the available study data."

  Response:

  The following text has been added to the draft labeling:

- FDA Comment (page 7, Description of Amenorrhea):
  "A more descriptive legend to the above figure should be proposed."

  Response:

  1) The legends have been modified to include the number of patients in each Regimen (A or B). For completers, the legend now reads, :

Clinical Studies-Information Regarding Lipids Effects-subsection (page 7):

- The number of patients in the clinical trial has been added. The section now reads:

Precautions-General subsection:

- FDA comment (page 15):
  "Insert number studied in the trial."

  Response:

  The text has been modified to state:

Adverse Reactions section:

- FDA Comment (page 18):

  Please propose a table of adverse events regardless of causality that occurred in ≥5% by treatment group.

Response:

The draft labeling has been revised to include a chart of adverse events as requested by the Agency (see Attachment 3).

In support of this amendment, provided herewith are four copies of annotations to FDA's proposals dated December 18, 1997 (Attachments 2-3) as well as an annotated copy of the Agency's revisions, as supplied in FDA's December 18, 1997 letter (Attachment 4).

We trust that you will find this revised draft labeling satisfactory and will approve supplemental application S-006 at your earliest convenience. We will have the appropriate Wyeth-Ayerst personnel available for a teleconference to discuss our proposals and to assist in obtaining approval by the User Fee date of January 8, 1998, if feasible.

Should you have any questions regarding this information, please contact the undersigned at (610) 902-3740 or Mr. Robert Quinty at (610) 902-3789.

Sincerely,
WYETH-AYERST LABORATORIES

Joseph S. Sonk, Senior Director
Women's Healthcare
U.S. Regulatory Affairs

c.c.: Ms. Diane Moore, CSO, FDA
Heidi Jolson, M.D, DRUDP, FDA
Theresa Van der Vlugt, M.D., DRUDP, FDA
rhq:/soo6a

DUPLICATE

WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

NDA SUPP AMEND
SEQ-006
SAC

NDA No. 20-527/S-006
Prempro™ Tablets

December 19, 1997

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Document Control Room 17B-20
Food and Drug Administration (HFD-580)
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Rarick:

Reference is made to our approved New Drug Application No. 20-527 for Prempro (conjugated estrogens/medroxyprogesterone acetate) tablets. Reference is also made to pending supplemental application S-006 that provides for a continuous 0.625mg conjugated estrogens/5 mg medroxyprogesterone acetate, "Prempro" dosing regimen.

Further reference is made to FDA's letter dated December 18, 1997 and received by Wyeth-Ayerst on December 18, 1997 which provided comprehensive comments on this supplemental application.

The purpose of this communication is to notify the Agency of our intent to amend this supplemental application in response to your December 18, 1997 letter, in accordance with 21 CFR 314.20(a)(1).

Sincerely,
WYETH-AYERST LABORATORIES

Joan E Barton

Joan E. Barton, Associate Director
Women's Health Care Products
Drug Regulatory Affairs

:rhq:s006

DUPLICATE

WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

ORIG AMENDMENT
SEP-006 BE

NDA No. 20-527/S-006
PREMPRO™ (conjugated estrogens/medroxyprogesterone acetate) Tablets

June 2, 1997

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

TRANSMITTED VIA FACSIMILE

Dear Dr. Rarick:

Reference is made to our approved New Drug Application No. 20-527 for PREMPRO (conjugated estrogens/medroxyprogesterone acetate) Tablets. Further reference is made to supplemental application NDA No. 20-527/S-006 dated January 8, 1997 that provides for a continuous combined dosing regimen of 0.625mg conjugated estrogens(CE)/5 mg medroxyprogesterone acetate(MPA) for PREMPRO Tablets. Reference is also made to a May 15, 1997 telephone conversation between Ms. Diane Moore, CSO, FDA and Mr. Robert Quinty of Wyeth-Ayerst in which Ms. Moore asked three specific questions regarding Attachment II (Continuous Combined Hormone Replacement Therapy Study: Market Research Study of Physician Use of 5 mg Progestin in Combination With Estrogen) of supplemental application NDA No. 20-527/S-006.

The purpose of this communication is to provide responses to the questions asked by the Agency in regard to the above-referenced supplemental application. For the reviewer's convenience, the questions asked by the Agency in the above-referenced telephone conversation are denoted by boldfaced type in the attached document. The response to each question immediately follows each question (Attachment A).

In addition, the number of physicians selected from the Xponent database is actually 20,000 and not the 6,000 as erroneously described in Attachment II, pages 36 and 45 of the January 8, 1997 supplemental application S-006 (see Attachment B). 10,000 from each specialty (OB/GYN and PCP) were selected at random. The response to the second question in the enclosed Attachment 1 reflects these corrected values and these corrected values do not affect the other data and do not affect the conclusions in Attachment II of the above-referenced January 8, 1997 submission.

We trust that you will find this information satisfactory and this supplemental application may be approved at the Agency's earliest convenience. Should you have any questions regarding this information, please call the undersigned at (610) 902-3772 or Mr. Robert Quinty at (610) 902-3789.

Sincerely,
WYETH-AYERST LABORATORIES

Joan E Barton

Joan E. Barton, Associate Director
Women's Health Care Products
U.S. Drug Regulatory Affairs

RHQ:\20527s06
C.C.: Ms. Diane Moore, CSO

ORIGINAL

WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

NDA No. 20-527/S-006
Prempro™/Premphase® Tablets

Noted
Z.B. vanderVliet
4/17/97

ORIG AMENDMENT
SE2-006 BC

April 2, 1997

Lisa Rarick, M.D., Director
Division of Reproductive
and Urologic Drug Products (HFD-580)
Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Noted
K Rarick
4/29/97

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

VIA FEDERAL EXPRESS

Dear Dr. Rarick:

Reference is made to our approved New Drug Application No. 20-527 for PREMPRO™ (conjugated estrogens/medroxyprogesterone acetate) Tablets. Further reference is made to our supplemental application, S-006 submitted to the Agency on January 8, 1997 which provides for the continuous combined dosing regimen of 0.625 mg conjugated estrogens (CE)/5 mg medroxyprogesterone acetate (MPA) for PREMPRO Tablets.

Reference is also made to a February 26, 1997 telephone conversation between the Agency's Dr. R. Seevers and Wyeth-Ayerst's Ms. JoAnne Bissinger in which Dr. Seevers requested an updated Environmental Assessment.

The purpose of this communication is to amend supplemental application NDA No. 20-527/S-006 to provide an updated Environmental Assessment as requested by Dr. Seevers. Additionally, we are providing a revised Stability Expiration Dating page to the NDA to include a 36 month expiration dating period for the continuous combined dosing regimen of 0.625 mg conjugated estrogens (CE)/5 mg medroxyprogesterone acetate (MPA) for PREMPRO Tablets. The 36 month expiration dating period for this regimen was provided for in the original NDA submission.

In support of this amendment, the following information is enclosed:

Attachment I.	Confidential Environmental Assessment Information
Attachment II.	Revised NDA Stability Expiration Dating page.

CENTER FOR DRUG
REC'D
APR 0 3 1997
HFD-580
ENVIRONMENTAL ASSESSMENT PROCESSED

Noted
RWS
4/29/97

We trust that you will find this information acceptable and that this supplemental application may be approved at your earliest convenience. Should you have any questions regarding this information, please contact the undersigned at (610) 902-3772 or Mr. Robert Quinty at (610) 902-3789.

Sincerely,
WYETH-AYERST LABORATORIES

Joan E. Barton

Joan E. Barton, Associate Director
Women's Health Care Products
U.S. Drug Regulatory Affairs

RHQ:/040202