CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20527/S013

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter			X	
Final Printed Labeling		X		
Medical Review(s)			X	
Chemistry Review(s)	X			
EA/FONSI			X	
Pharmacology Review(s)			X	
Statistical Review(s)			X	
Microbiology Review(s)			X	
Clinical Pharmacology Biopharmaceutics Review(s)			X	
Bioequivalence Review(s)			X	
Administrative Document(s)			X	
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20527/S013

Trade Name: Prempro/Premphase Tablets

Generic Name: (conjugated estrogens/medroxyprogesterone acetate)

Sponsor: Wyeth-Ayerst Research

Approval Date: May 12, 1998

INDICATION: Provides for the incorporation of Premphase information into the current Prempro labeling.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number:NDA 20527/S013

APPROVAL LETTER

NDA 20-527/S-013

MAY 12 1998

Wyeth-Ayerst Research
Attention: Joseph S. Sonk, Ph.D.
Senior Director
Women's Health Care Products
U.S. Drug Regulatory Affairs
P. O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Sonk:

Please refer to your supplemental new drug application dated January 23, 1998, received January 26, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prempro/Premphase (conjugated estrogens/medroxyprogesterone acetate) Tablets.

The supplemental application provides for the incorporation of Premphase information into the current Prempro labeling. Further revisions are provided to the combined Prempro and Premphase physician and patient package inserts to strengthen the **WARNINGS** and **PRECAUTIONS** sections of the physician package insert and the **Abnormal blood clotting** subsection of **THE RISKS OF ESTROGENS AND/OR PROGESTINS** section of the patient package insert regarding thromboembolic disease in women as well as the incorporation of the 0.625 mg/5.0 mg dose for the 5 mg MPA continuous dosing regimen.

We have completed the review of this supplemental application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the draft labeling in the submission dated January 23, 1998, with the revision listed below. Accordingly, the supplemental application is approved effective on the date of this letter. The revision is as follows:

These revisions are terms of the supplemental NDA approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 20-527/S-013. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drugs become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package inserts directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Should a letter communicating important information about these drug products (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20527/S013

CHEMISTRY REVIEW(S)

ORIGINAL

APR 27 1998

CHEMIST'S REVIEW

1. Organization
DRUDP HFD-580

2. NDA Number
20-527

3. Name and Address of Applicant
Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299

4. Supplement
SLR-013
23-JAN-98

5. Name of Drug
Prempro/Premphase Tablets

6. Nonproprietary Name
Conjugated estrogens/medroxyprogesterone acetate

7 Supplement Provides For
To incorporate Premphase information into the current Prempro labeling.

8. Amendment

9. Pharmacological Category
Hormone replacement therapy

10. How Dispensed
RX

11. Related

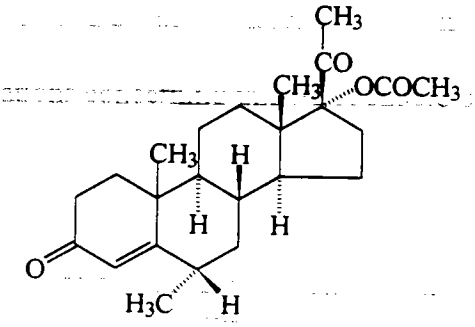
12. Dosage form
Tablets

13. Potency
0.625 mg conjugated estrogens and 2.5 or 5 mg medroxyprogesterone acetate

14. Chemical Name and Structure

1. Conjugated estrogens: see USP 23

2. Medroxyprogesterone acetate: Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, (6α)-



15. Comments
The molecular formula, molecular weight and chemical structure of medroxyprogesterone acetate should be included in the Description section of the printed labeling. This request is supported under 21 CFR 201.57(a)(1)(vi) and 21 CFR 201.57(a)(2). Although this may seem to be inconsistent with not requiring the same information for the conjugated estrogens component of the drug product, this is not the case. The conjugated estrogens component is in actuality a complex mixture of estrogens and other steroids whereas the medroxyprogesterone acetate component is a single well-characterized chemical compound.

16. Conclusion and Recommendation

This supplement is approvable pending resolution of the above issue.

17. Name	**Reviewer's Signature**	**Date**
David T. Lin, Ph.D. Review Chemist	/S/ 4/27/98	25-MAR-98 27-APR-98 revised

cc:
Orig. NDA #20-527
HFD-580/Division File
HFD-580/DMoore
HFD-580/MRhee/DLin

R/D Init by: MJ Rhee /S/ 4/27/98

Filename: S20527.013(doc)

ORIGINAL APR 1 1998

CHEMIST'S REVIEW

1. Organization
DRUDP HFD-580

2. NDA Number
20-527

3. Name and Address of Applicant
Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299

4. Supplement
SLR-014
23-JAN-98

5. Name of Drug
Prempro/Premphase Tablets

6. Nonproprietary Name
Conjugated estrogens/medroxyprogesterone acetate

7 Supplement Provides For
To incorporate Premphase information into the current Prempro labeling.

8. Amendment

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Hormone replacement therapy

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RX

11. Related

12. Dosage form
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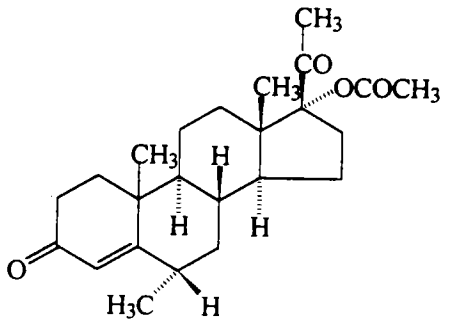

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David T. Lin, Ph.D. Review Chemist	/S/ 4/1/98	25-MAR-98 01-APR-98 revised

cc:
Orig. NDA #20-527
HFD-580/Division File
HFD-580/DMoore
HFD-580/MRhee/DLin

R/D Init by: MJ Rhee /S/ 4/1/98

Filename: S20527.014(doc)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20527/S013

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-527/S-014

FEB 27 1998

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

Attention: Joseph S. Sonk, Ph.D.,
Senior Director

Dear Dr. Sonk :

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Prempro/ Premphase
NDA Number:	20-527
Supplement Number:	S-013
Date of Supplement:	January 23, 1998
Date of Receipt:	January 26, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on March 27, 1998 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

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

cc:
Original NDA 20-527/S-014
HFD-580/Div. Files
HFD-580/CSO/D. Moore

SUPPLEMENT ACKNOWLEDGEMENT

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-527/S-014

FEB 27 1998

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

Attention: Joseph S. Sonk, Ph.D.,
Senior Director

Dear Dr. Sonk :

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Prempro/ Premphase
NDA Number:	20-527
Supplement Number:	S-013
Date of Supplement:	January 23, 1998
Date of Receipt:	January 26, 1998

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All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

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

cc:
Original NDA 20-527/S-014
HFD-580/Div. Files
HFD-580/CSO/D. Moore

SUPPLEMENT ACKNOWLEDGEMENT