CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-527/S-024, S-026, S-031

Trade Name: PREMPRO/PREMPHASE

Generic Name: Conjugated estrogens/medroxyprogesterone acetate tablets

Sponsor: Wyeth Pharmaceuticals

Approval Date: June 4, 2003

Indications: For the treatment of moderate-to-severe vasomotor symptoms associated with the menopause, the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy associated with the menopause, and the prevention of postmenopausal osteoporosis.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-527/S-024, S-026, S-031

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	X
Labeling	X
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	X
Pharmacology Review(s)	
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-527/S-024, S-026, S-031

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-527/S-024, S-026, S-031

Wyeth Pharmaceuticals
Attention: Jennifer D. Norman, R.Ph.
Associate Director, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Norman:

Please refer to your supplemental new drug applications dated November 5, 2001, received November 7, 2001, (S-024) April 30, 2002, received May 1, 2002, (S-026) and February 11, 2003 received February 13, 2003, (S-031) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PREMPRO™/PREMPHASE® (conjugated estrogens/medroxyprogesterone acetate tablets).

We acknowledge receipt of your submissions dated October 15, 2002, March 13, April 2 and 7, and May 28 and 30, 2003 to S-024. Your March 13, 2003 submission constituted a complete response to our approvable letter of August 28, 2002.

We acknowledge receipt of your submissions dated November 27and December 5, 2002, April 2 and 7, and May 28 and 30, 2003 to S-026. Your November 27, 2002 submission constituted a complete response to our approvable letter of July 24, 2002.

We also acknowledge receipt of your submissions dated May 22, 28 and 30, 2003 to S-031.

These supplemental new drug applications provide for:

1. An additional strength of PREMPRO™ (0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate) continuous combined regimen for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause, and the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. (S-024)

2. The use of PREMPRO™ (0.45 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate and 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate) for the prevention of postmenopausal osteoporosis. (S-026)

3. To provide for revisions in the text of the **DESCRIPTION, CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, HOW SUPPLIED** and **PATIENT INFORMATION** sections of the direction circular. (S-031)

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text (attached).

We remind you of our agreements that were made in your submission dated April 2, 2003. These agreements are listed below.

1. You have agreed to an interim release and stability specification for CE dissolution at the (b) (4) timepoint. This interim acceptance criterion is (b) (4)
2. You have committed to a Dissolution Surveillance Program for the dissolution of conjugated estrogens in the PREMPRO ™ 0.3 mg/1.5 mg drug product. In this commitment, every packaged lot will be tested for CE dissolution at six-month intervals. This surveillance program will be performed through expiration of the product.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper 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/these submission(s) should be designated "FPL for approved supplement NDA 20-527/S-024, S-026 and S-031." Approval of these submissions by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kassandra Sherrod, R.Ph., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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

/s/

Daniel A. Shames
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-527/S-024, S-026, S-031

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-527

APPROVABLE LETTER

Wyeth-Ayerst
Attention: Jennifer D. Norman, R. Ph.
Associate Director, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Norman:

Please refer to your supplemental new drug application dated November 5, 2001 received November 7, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prempro™ (conjugated estrogens/medroxyprogesterone acetate tablets) and Premphase® (conjugated estrogens/medroxyprogesterone acetate tablets).

We also acknowledge receipt of your submissions dated January 25, March 5, and 7, April 29, and July 8, 2002.

This supplemental new drug application provides for an additional strength of Prempro™ (0.3 mg conjugated estrogen/1.5 mg medroxyprogesterone acetate) continuous combined regimen for the treatment of moderate-to-severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy.

We have completed our review of this application and it is approvable. Before the application may be approved, however, you must address the following deficiencies:

Chemistry
The Wyeth Laboratories facility in Rouses Point, NY must have a satisfactory cGMP inspection. In addition, all facilities listed in this application must be in cGMP compliance.

Labeling

1. Submit draft labeling identical in content to the enclosed revised labeling (text for the package insert, text for the patient package insert). Additions are delineated with double underlining, deletions are delineated with ~~strikeouts~~ and comments are delineated with **14-Font BOLD** script.

2. On July 9, 2002, the National Heart Lung and Blood Institute's (NHLBI) Women's Health Initiative (WHI) published the findings of the unfavorable benefit to risk profile of Prempro (conjugated equine estrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day) for primary prevention of coronary heart disease. The FDA is reviewing these findings and their possible implications for the approved indications, as well as your proposed language, submitted in the "changes being effected" supplement, for NDA 20-527/S 029, to address the WHI results. Revision to the enclosed labeling may be required as a result of these ongoing reviews.

Likewise should any other information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required. All previous revisions, as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of

these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes before approval of this supplemental application.

If you have any questions, call Dornette Spell-LeSane, NP-C, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

87 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

___X___ Draft Labeling (b4)

___X___ Draft Labeling (b5)

_____ Deliberative Process (b5)

_____ Law Enforcement Action (b7)

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/s/

Daniel A. Shames
8/28/02 04:08:49 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-527/S-024, S-026, S-031

LABELING

®

PREMPRO™
(conjugated estrogens/medroxyprogesterone acetate tablets)
PREMPHASE®
(conjugated estrogens/medroxyprogesterone acetate tablets)

Rx only

WARNING

Estrogens and progestins should not be used for the prevention of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during 5 years of treatment with conjugated equine estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (see **CLINICAL PHARMACOLOGY, Clinical Studies**). Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

PREMPRO™ 0.3 mg/1.5 mg therapy consists of a single tablet containing 0.3 mg of the conjugated estrogens (CE) found in Premarin® tablets and 1.5 mg of medroxyprogesterone acetate (MPA) for oral administration.

PREMPRO 0.45 mg/1.5 mg therapy consists of a single tablet containing 0.45 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg of medroxyprogesterone acetate for oral administration.

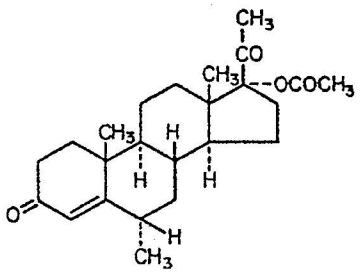
PREMPRO 0.625 mg/2.5 mg therapy consists of a single tablet containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 2.5 mg of medroxyprogesterone acetate for oral administration.

PREMPRO 0.625 mg/5.0 mg therapy consists of a single tablet containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration.

PREMPHASE® therapy consists of two separate tablets, a maroon Premarin tablet containing 0.625 mg of conjugated estrogens that is taken orally on days 1 through 14 and a light-blue tablet containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate that is taken orally on days 15 through 28.

The conjugated equine estrogens found in Premarin tablets are a mixture of sodium estrone sulfate and sodium equilin sulfate. They contain as concomitant components, as sodium sulfate conjugates, 17 α-dihydroequilin, 17 α-estradiol and 17 β-dihydroequilin.

Medroxyprogesterone acetate is a derivative of progesterone. It is a white to off-white, odorless, crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and in dioxane, sparingly soluble in alcohol and in methanol, slightly soluble in ether, and insoluble in water. The chemical name for MPA is pregn-4-ene-3, 20-dione, 17-(acetyloxy)-6-methyl-, (6α)-. Its molecular formula is $C_{24}H_{34}O_4$, with a molecular weight of 386.53. Its structural formula is:



PREMPRO 0.3 mg/1.5 mg
Each cream tablet for oral administration contains 0.3 mg conjugated estrogens, 1.5 mg medroxyprogesterone acetate, and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, yellow ferric oxide.

PREMPRO 0.45 mg/1.5 mg
Each gold tablet for oral administration contains 0.45 mg conjugated estrogens, 1.5 mg medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, yellow ferric oxide.

PREMPRO 0.625 mg/2.5 mg
Each peach tablet for oral administration contains 0.625 mg conjugated estrogens, 2.5 mg of medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, red ferric oxide.

PREMPRO 0.625 mg/5 mg
Each light-blue tablet for oral administration contains 0.625 mg conjugated estrogens, 5 mg of medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, FD&C Blue No. 2.

PREMPHASE
Each maroon Premarin tablet for oral administration contains 0.625 mg of conjugated estrogens and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, stearic acid, sucrose, titanium dioxide, FD&C Blue No. 2, D&C Red No. 27, FD&C Red No. 40. These tablets comply with USP Drug Release Test 1.

Each light-blue tablet for oral administration contains 0.625 mg of conjugated estrogens and 5 mg of medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, FD&C Blue No. 2.

CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

Parenterally administered medroxyprogesterone acetate (MPA) inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation, although available data indicate that this does not occur when the usually recommended oral dosage is given as single daily doses. MPA may achieve its beneficial effect on the endometrium in part by decreasing nuclear estrogen receptors and suppression of epithelial DNA synthesis in endometrial tissue. Androgenic and anabolic effects of MPA have been noted, but the drug is apparently devoid of significant estrogenic activity.

Pharmacokinetics

Absorption

Conjugated estrogens are soluble in water and are well absorbed from the gastrointestinal tract after release from the drug formulation. However, PREMPRO and PREMPHASE contain a formulation of medroxyprogesterone acetate (MPA) that is immediately released and conjugated estrogens that are slowly released over several hours. MPA is well absorbed from the gastrointestinal tract. Table 1 summarizes the mean pharmacokinetic parameters for unconjugated and conjugated estrogens, and medroxyprogesterone acetate following administration of 2 PREMPRO 0.625 mg/2.5 mg and 2 PREMPRO 0.625 mg/5 mg tablets to healthy postmenopausal women.

Table 1. PHARMACOKINETIC PARAMETERS FOR UNCONJUGATED AND CONJUGATED ESTROGENS (CE) AND MEDROXYPROGESTERONE ACETATE (MPA)

DRUG	2 x 0.625 mg CE/2.5 mg MPA Combination Tablets (n=54)				2 x 0.625 mg CE/5 mg MPA Combination Tablets (n=51)			
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (pg/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (pg•h/mL)	**C_{max}** (pg/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (pg•h/mL)
Unconjugated Estrogens								
Estrone	175 (23)	7.6 (24)	31.6 (23)	5358 (34)	124 (43)	10 (35)	62.2 (137)	6303 (40)
BA* -Estrone	159 (26)	7.6 (24)	16.9 (34)	3313 (40)	104 (49)	10 (35)	26.0 (100)	3136 (51)
Equilin	71 (31)	5.8 (34)	9.9 (35)	951 (43)	54 (43)	8.9 (34)	15.5 (53)	1179 (56)
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Conjugated Estrogens								
Total Estrone	6.6 (38)	6.1 (28)	20.7 (34)	116 (59)	6.3 (48)	9.1 (29)	23.6 (36)	151 (42)
BA* -Total Estrone	6.4 (39)	6.1 (28)	15.4 (34)	100 (57)	6.2 (48)	9.1 (29)	20.6 (35)	139 (40)
Total Equilin	5.1 (45)	4.6 (35)	11.4 (25)	50 (70)	4.2 (52)	7.0 (36)	17.2 (131)	72 (50)
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Medroxyprogesterone Acetate								
MPA	1.5 (40)	2.8 (54)	37.6 (30)	37 (30)	4.8 (31)	2.4 (50)	46.3 (39)	102 (28)

BA* = Baseline adjusted
C_{max} = peak plasma concentration
t_{max} = time peak concentration occurs
$t_{1/2}$ = apparent terminal-phase disposition half-life (0.693/• z)
AUC = total area under the concentration-time curve

Table 2 summarizes the mean pharmacokinetic parameters for unconjugated and conjugated estrogens and medroxyprogesterone acetate following administration of 2 PREMPRO 0.45 mg/1.5 mg and 2 PREMPRO 0.3 mg/1.5 mg tablets to healthy, postmenopausal women.

Table 2. PHARMACOKINETIC PARAMETERS FOR UNCONJUGATED AND CONJUGATED ESTROGENS (CE) AND MEDROXYPROGESTERONE ACETATE (MPA)								
DRUG	2 x 0.3 mg CE/1.5 mg MPA Combination (n = 30)				2 x 0.45 mg CE/1.5 mg MPA Combination (n = 61)			
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (pg/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (pg•h/mL)	**C_{max}** (pg/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (pg•h/mL)
Unconjugated Estrogens								
Estrone	79	9.4	51.3	5029	91	9.8	48.9	5786
	(35)	(86)	(30)	(45)	(30)	(47)	(28)	(42)
BA* -Estrone	56	9.4	19.8	1429	67	9.8	21.5	2042
	(46)	(86)	(39)	(49)	(37)	(47)	(49)	(52)
Equilin	30	7.9	14.0	590	35	8.5	16.4	825
	(43)	(42)	(75)	(42)	(40)	(34)	(49)	(44)
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Conjugated Estrogens								
Total Estrone	2.4	7.1	26.5	62	3.0	8.2	25.9	78
	(38)	(27)	(33)	(48)	(37)	(39)	(23)	(40)
BA* -Total	2.2	7.1	16.3	41	2.8	8.2	16.9	56
Estrone	(36)	(27)	(32)	(44)	(36)	(39)	(36)	(39)
Total Equilin	1.5	5.5	11.5	22	1.9	7.2	12.2	31
	(47)	(29)	(24)	(41)	(42)	(33)	(25)	(52)
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Medroxyprogesterone Acetate								
MPA	1.2	2.8	42.3	29.4	1.2	2.7	47.2	32.0
	(42)	(61)	(34)	(30)	(42)	(52)	(41)	(36)

BA* = Baseline adjusted
C_{max} = peak plasma concentration
t_{max} = time peak concentration occurs
$t_{1/2}$ = apparent terminal-phase disposition half-life (0.693/• $\frac{}{z}$)
AUC = total area under the concentration-time curve

Food-Effect: Single dose studies in healthy, postmenopausal women were conducted to investigate any potential drug interaction when PREMPRO or PREMPHASE is administered with a high fat breakfast. Administration with food decreased the C_{max} of total estrone by 18 to 34% and increased total equilin C_{max} by 38% compared to the fasting state, with no other effect on the rate or extent of absorption of other conjugated or unconjugated estrogens. Administration with food approximately doubles MPA C_{max} and increases MPA AUC by approximately 20 to 30%.

Dose Proportionality: The C_{max} and AUC values for MPA observed in two separate pharmacokinetic studies conducted with 2 PREMPRO 0.625 mg/2.5 mg or 2 PREMPRO or PREMPHASE 0.625 mg/5 mg tablets exhibited nonlinear dose proportionality; doubling the MPA dose from 2 x 2.5 to 2 x 5.0 mg increased the mean C_{max} and AUC by 3.2 and 2.8 folds, respectively.

The dose proportionality of estrogens and medroxyprogesterone acetate was assessed by combining pharmacokinetic data across another two studies totaling 61 healthy, postmenopausal women. Single conjugated estrogens doses of 2 x 0.3 mg, 2 x 0.45 mg, or 2 x 0.625 mg were administered either alone or in combination with medroxyprogesterone acetate doses of 2 x 1.5 mg or 2 x 2.5 mg. Most of the estrogen components demonstrated dose proportionality; however, several estrogen components did not. Medroxyprogesterone acetate pharmacokinetic parameters increased in a dose-proportional manner.

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin. MPA is approximately 90% bound to plasma proteins but does not bind to SHBG.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women a significant proportion of the circulating estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens. Metabolism and elimination of MPA occurs primarily in the liver via hydroxylation, with subsequent conjugation and elimination in the urine.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Most metabolites of MPA are excreted as glucuronide conjugates with only minor amounts excreted as sulfates.

Special Populations

No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

Drug Interactions

Data from a single-dose drug-drug interaction study involving conjugated estrogens and medroxyprogesterone acetate indicate that the pharmacokinetic disposition of both drugs is not altered when the drugs are coadministered. No other clinical drug-drug interaction studies have been conducted with conjugated estrogens.

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Clinical Studies

Effects on vasomotor symptoms

In the first year of the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, a total of 2805 postmenopausal women (average age 53.3 ± 4.9 years) were randomly assigned to one of eight treatment groups of either placebo or conjugated estrogens with or without medroxyprogesterone acetate. Efficacy for vasomotor symptoms was assessed during the first 12 weeks of treatment in a subset of symptomatic women (n = 241) who had at least 7 moderate to severe hot flushes daily or at least 50 moderate to severe hot flushes during the week before randomization. PREMPRO 0.625 mg/2.5 mg, 0.45 mg/1.5 mg, and 0.3 mg/1.5 mg were shown to be statistically better than placebo at weeks 4 and 12 for relief of both the frequency and severity of moderate to severe vasomotor symptoms. Table 3 shows the adjusted mean number of hot flushes in the PREMPRO 0.625 mg/2.5 mg, 0.45 mg/1.5 mg, 0.3 mg /1.5 mg, and placebo groups during the initial 12-week period.

Table 3: SUMMARY TABULATION OF THE NUMBER OF HOT FLUSHES PER DAY – MEAN VALUES AND COMPARISONS BETWEEN THE ACTIVE TREATMENT GROUPS AND THE PLACEBO GROUP – PATIENTS WITH AT LEAST 7 MODERATE TO SEVERE FLUSHES PER DAY OR AT LEAST 50 PER WEEK AT BASELINE, LOCF

Treatment[a] (No. of Patients) Time Period (week)	No. of Hot Flushes/Day Baseline Mean ± SD	Observed Mean ± SD	Mean Change ± SD	p-Values vs. Placebo[b]
0.625 mg/2.5 mg (n = 34)				
4	11.98 ± 3.54	3.19 ± 3.74	-8.78 ± 4.72	<0.001
12	11.98 ± 3.54	1.16 ± 2.22	-10.82 ± 4.61	<0.001
0.45mg/1.5mg (n = 29)				
4	12.61 ± 4.29	3.64 ± 3.61	-8.98 ± 4.74	<0.001
12	12.61 ± 4.29	1.69 ± 3.36	-10.92 ± 4.63	<0.001
0.3 mg/1.5 mg (n = 33)				
4	11.30 ± 3.13	3.70 ± 3.29	-7.60 ± 4.71	<0.001
12	11.30 ± 3.13	1.31 ± 2.82	-10.00 ± 4.60	<0.001
Placebo (n = 28)				
4	11.69 ± 3.87	7.89 ± 5.28	-3.80 ± 4.71	-
12	11.69 ± 3.87	5.71 ± 5.22	-5.98 ± 4.60	-

a: Identified by dosage (mg) of Premarin/MPA or placebo.
b. There were no statistically significant differences between the 0.625 mg/2.5 mg, 0.45 mg/1.5 mg, and 0.3 mg/1.5 mg groups at any time period.

Effects on vulvar and vaginal atrophy

Results of vaginal maturation indexes at cycles 6 and 13 showed that the differences from placebo were statistically significant ($p < 0.001$) for all treatment groups (conjugated estrogens alone and conjugated estrogens/medroxyprogesterone acetate treatment groups).

Effects on the endometrium

In a 1-year clinical trial of 1376 women (average age 54.0 ± 4.6 years) randomized to PREMPRO 0.625 mg/2.5 mg (n=340), PREMPRO 0.625 mg/5 mg (n=338), PREMPHASE 0.625 mg/5 mg (n=351), or Premarin 0.625 mg alone (n=347), results of evaluable biopsies at 12 months (n=279, 274, 277, and 283, respectively) showed a reduced risk of endometrial hyperplasia in the two PREMPRO treatment groups (less than 1%) and in the PREMPHASE treatment group (less than 1%; 1% when focal hyperplasia was included) compared to the Premarin group (8%; 20% when focal hyperplasia was included). See Table 4.

Table 4. INCIDENCE OF ENDOMETRIAL HYPERPLASIA AFTER ONE YEAR OF TREATMENT

	Groups			
	PREMPRO 0.625 mg/2.5 mg	PREMPRO 0.625 mg/5 mg	PREMPHASE 0.625 mg/5 mg	Premarin 0.625 mg
Total number of patients	340	338	351	347
Number of patients with evaluable biopsies	279	274	277	283
No. (%) of patients with biopsies				
• all focal and non-focal hyperplasia	2 (<1)*	0 (0)*	3 (1)*	57 (20)
• excluding focal cystic hyperplasia	2 (<1)*	0 (0)*	1 (<1)*	25 (8)

*Significant ($p < 0.001$) in comparison with Premarin (0.625 mg) alone.

In the first year of the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, 2001 women (average age 53.3 ± 4.9 years) of whom 88% were Caucasian were treated with either Premarin 0.625 mg alone (n = 348), Premarin 0.45 mg alone (n = 338), Premarin 0.3 mg alone (n = 326) or PREMPRO 0.625 mg/2.5 mg (n = 331), PREMPRO 0.45 mg/1.5 mg (n = 331) or PREMPRO 0.3 mg/1.5 mg (n = 327). Results of evaluable endometrial biopsies at 12 months showed a reduced risk of endometrial hyperplasia or cancer in the PREMPRO treatment groups compared with the corresponding Premarin alone treatment groups, except for the PREMPRO 0.3 mg /1.5 mg and Premarin 0.3 mg alone groups, in each of which there was only 1 case. See Table 5.

No endometrial hyperplasia or cancer was noted in those patients treated with the continuous combined regimens who continued for a second year in the osteoporosis and metabolic substudy of the HOPE study. See Table 6.

Table 5. INCIDENCE OF ENDOMETRIAL HYPERPLASIA/CANCER[a] AFTER ONE YEAR OF TREATMENT[b]

	Groups					
Patient	Prempro 0.625 mg/2.5 mg	Premarin 0.625 mg	Prempro 0.45 mg/1.5 mg	Premarin 0.45 mg	Prempro 0.3 mg/1.5 mg	Premarin 0.3 mg
Total number of patients	331	348	331	338	327	326
Number of patients with evaluable biopsies	278	249	272	279	271	269
No. (%) of patients with biopsies						
• hyperplasia/cancer[a] (consensus[c])	0 (0)[d]	20 (8)	1 (< 1)[a,d]	9 (3)	1 (< 1)[e]	1 (<1)[a]

a: All cases of hyperplasia/cancer were endometrial hyperplasia except for 1 patient in the Premarin 0.3 mg group diagnosed with endometrial cancer based on endometrial biopsy, and 1 patient in the Premarin/MPA 0.45 mg/1.5 mg group diagnosed with endometrial cancer based on endometrial biopsy.

b: Two (2) primary pathologists evaluated each endometrial biopsy. Where there was lack of agreement on the presence or absence of hyperplasia/cancer between the two, a third pathologist adjudicated (consensus).

c. For an endometrial biopsy to be counted as consensus endometrial hyperplasia or cancer, at least 2 pathologists had to agree on the diagnosis.

d: Significant ($p < 0.05$) in comparison with corresponding dose of Premarin alone.

e: Non-significant in comparison with corresponding dose of Premarin alone.

TABLE 6. OSTEOPOROSIS AND METABOLIC SUBSTUDY, INCIDENCE OF ENDOMETRIAL HYPERPLASIA/CANCER[a] AFTER TWO YEARS OF TREATMENT[b]

	Groups					
Patient	Prempro 0.625 mg/2.5 mg	Premarin 0.625 mg	Prempro 0.45 mg/1.5 mg	Premarin 0.45 mg	Prempro 0.3 mg/1.5 mg	Premarin 0.3 mg
Total number of patients	75	65	75	74	79	73
Number of patients with evaluable biopsies	62	55	69	67	75	63
No. (%) of patients with biopsies						
• hyperplasia/cancer[a] (consensus[c])	0 (0)[d]	15 (27)	0 (0)[d]	10 (15)	0 (0)[d]	2 (3)

a: All cases of hyperplasia/cancer were endometrial hyperplasia in patients who continued for a second year in the osteoporosis and metabolic substudy of the HOPE study.

b: Two (2) primary pathologists evaluated each endometrial biopsy. Where there was lack of agreement on the presence or absence of hyperplasia/cancer between the two, a third pathologist adjudicated (consensus).

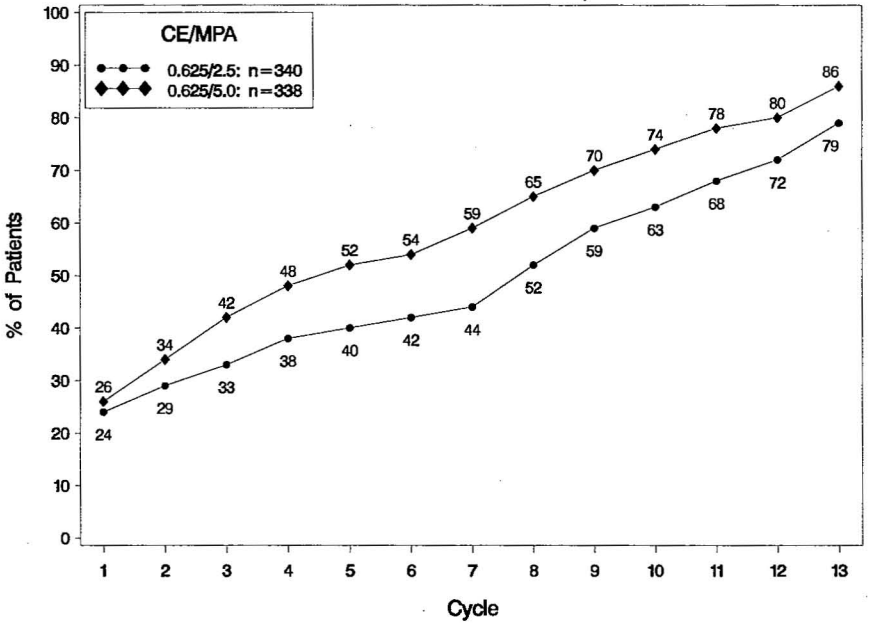
c. For an endometrial biopsy to be counted as consensus endometrial hyperplasia or cancer, at least 2 pathologists had to agree on the diagnosis.

d: Significant ($p < 0.05$) in comparison with corresponding dose of Premarin alone.

Effects on uterine bleeding or spotting:

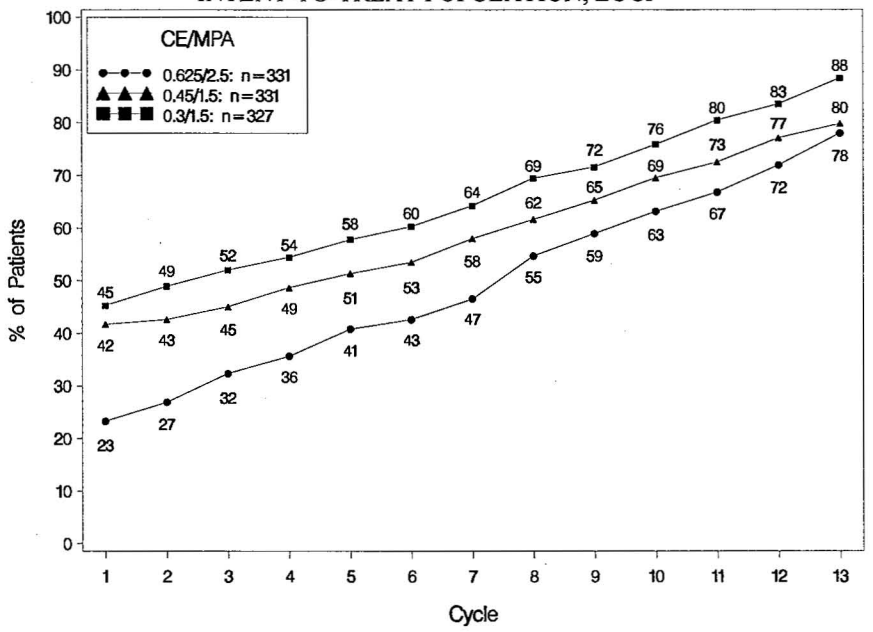
The effects of PREMPRO on uterine bleeding or spotting, as recorded on daily diary cards, were evaluated in 2 clinical trials. Results are shown in Figures 1 and 2.

FIGURE 1. PATIENTS WITH CUMULATIVE AMENORRHEA OVER TIME
PERCENTAGES OF WOMEN WITH NO BLEEDING OR SPOTTING
AT A GIVEN CYCLE THROUGH CYCLE 13
INTENT-TO-TREAT POPULATION, LOCF



Note: The percentage of patients who were amenorrheic in a given cycle and through cycle 13 is shown. If data were missing, the bleeding value from the last reported day was carried forward (LOCF).

FIGURE 2. PATIENTS WITH CUMULATIVE AMENORRHEA OVER TIME
PERCENTAGES OF WOMEN WITH NO BLEEDING OR SPOTTING
AT A GIVEN CYCLE THROUGH CYCLE 13
INTENT-TO-TREAT POPULATION, LOCF



Note: The percentage of patients who were amenorrheic in a given cycle and through cycle 13 is shown. If data were missing, the bleeding value from the last reported day was carried forward (LOCF).

Effects on bone mineral density

Health and Osteoporosis, Progestin and Estrogen (HOPE) Study

The HOPE study was a double-blind, randomized, placebo/active-drug-controlled, multicenter study of healthy postmenopausal women with an intact uterus. Subjects (mean age 53.3 ± 4.9 years) were 2.3 ± 0.9 years, on average, since menopause, and took one 600-mg tablet of elemental calcium (Caltrate) daily. Subjects were not given vitamin D supplements. They were treated with PREMPRO 0.625 mg/2.5 mg, 0.45 mg/1.5 mg or 0.3 mg/1.5 mg, comparable doses of Premarin alone, or placebo. Prevention of bone loss was assessed by measurement of bone mineral density (BMD), primarily at the anteroposterior lumbar spine (L_2 to L_4). Secondarily, BMD measurements of the total body, femoral neck, and trochanter were also analyzed. Serum osteocalcin, urinary calcium, and N-telopeptide were used as bone turnover markers (BTM) at cycles 6, 13, 19, and 26.

Intent-to-treat subjects

All active treatment groups showed significant differences from placebo in each of the 4 BMD endpoints. These significant differences were seen at cycles 6, 13, 19, and 26. With PREMPRO, the mean percent increases in the primary efficacy measure (L_2 to L_4 BMD) at the final on-therapy evaluation (cycle 26 for those who completed and the last available evaluation for those who discontinued early) were 3.28% with

0.625 mg/2.5 mg, 2.18% with 0.45 mg/1.5 mg, and 1.71% with 0.3 mg/1.5 mg. The placebo group showed a mean percent decrease from baseline at the final evaluation of 2.45%. These results show that the lower dose regimens of PREMPRO were effective in increasing L_2 to L_4 BMD compared with placebo and, therefore, support the efficacy of lower doses of PREMPRO.

The analysis for the other 3 BMD endpoints yielded mean percent changes from baseline in femoral trochanter that were generally larger than those seen for L_2 to L_4 and changes in femoral neck and total body that were generally smaller than those seen for L_2 to L_4. Significant differences between groups indicated that each of the PREMPRO treatment groups was more effective than placebo for all 3 of these additional BMD endpoints. With regard to femoral neck and total body, the continuous combined treatment groups all showed mean percent increases in BMD while the placebo group showed mean percent decreases. For femoral trochanter, each of the PREMPRO groups showed a mean percent increase that was significantly greater than the small increase seen in the placebo group. The percent changes from baseline to final evaluation are shown in Table 7.

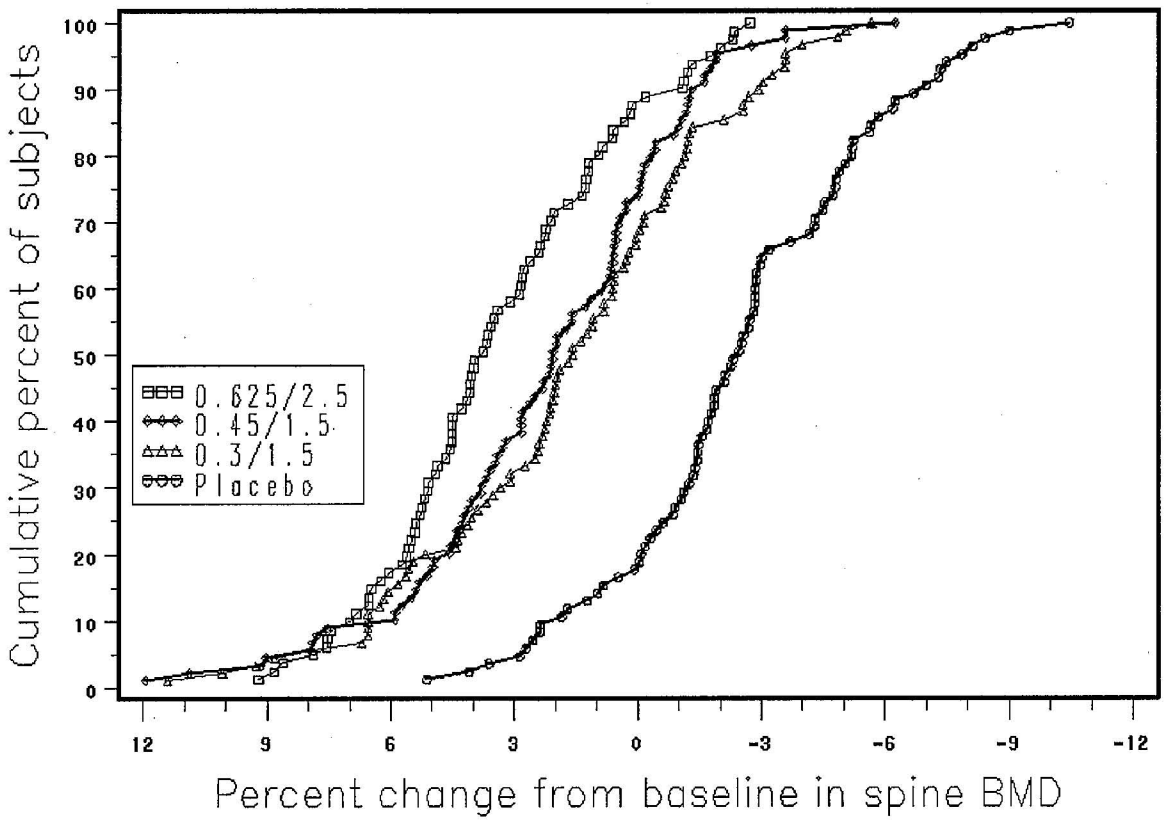
Table 7. PERCENT CHANGE IN BONE MINERAL DENSITY: COMPARISON BETWEEN ACTIVE AND PLACEBO GROUPS IN THE INTENT-TO-TREAT POPULATION, LAST OBSERVATION CARRIED FORWARD

Region Evaluated Treatment Group[a]	No. of Subjects	Baseline (g/cm^2) Mean ± SD	Change from Baseline (%) Adjusted Mean ± SE	p-Value vs Placebo
L_2 to L_4 BMD				
0.625/2.5	81	1.14 ± 0.16	3.28 ± 0.37	<0.001
0.45/1.5	89	1.16 ± 0.14	2.18 ± 0.35	<0.001
0.3/1.5	90	1.14 ± 0.15	1.71 ± 0.35	<0.001
Placebo	85	1.14 ± 0.14	-2.45 ± 0.36	
Total body BMD				
0.625/2.5	81	1.14 ± 0.08	0.87 ± 0.17	<0.001
0.45/1.5	89	1.14 ± 0.07	0.59 ± 0.17	<0.001
0.3/1.5	91	1.13 ± 0.08	0.60 ± 0.16	<0.001
Placebo	85	1.13 ± 0.08	-1.50 ± 0.17	
Femoral neck BMD				
0.625/2.5	81	0.89 ± 0.14	1.62 ± 0.46	<0.001
0.45/1.5	89	0.89 ± 0.12	1.48 ± 0.44	<0.001
0.3/1.5	91	0.86 ± 0.11	1.31 ± 0.43	<0.001
Placebo	85	0.88 ± 0.14	-1.72 ± 0.45	
Femoral trochanter BMD				
0.625/2.5	81	0.77 ± 0.14	3.35 ± 0.59	0.002
0.45/1.5	89	0.76 ± 0.12	2.84 ± 0.57	0.011
0.3/1.5	91	0.76 ± 0.12	3.93 ± 0.56	<0.001
Placebo	85	0.75 ± 0.12	0.81 ± 0.58	

a: Identified by dosage (mg/mg) of Premarin/MPA or placebo.

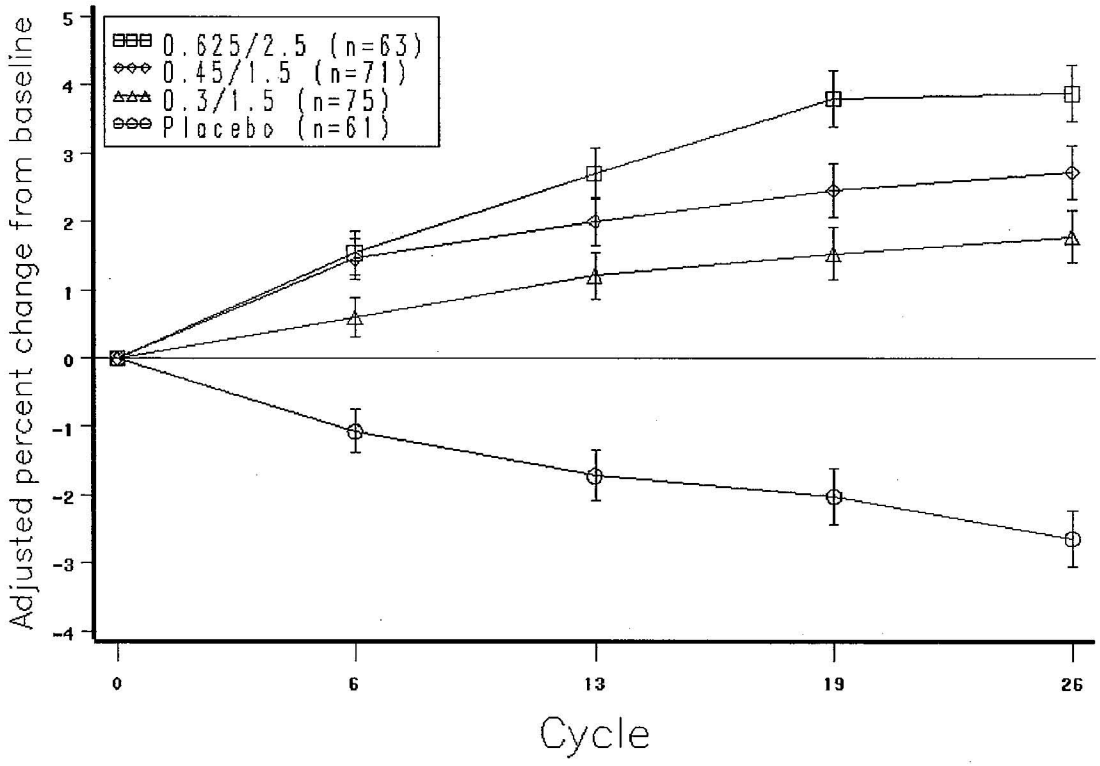
Figure 3 shows the cumulative percentage of subjects with percent changes from baseline in spine BMD equal to or greater than the percent change shown on the x-axis.

Figure 3. CUMULATIVE PERCENT OF SUBJECTS WITH CHANGES FROM BASELINE IN SPINE BMD OF GIVEN MAGNITUDE OR GREATER IN PREMARIN/MPA AND PLACEBO GROUPS



The mean percent changes from baseline in L_2 to L_4 BMD for women who completed the bone density study are shown with standard error bars by treatment group in Figure 4. Significant differences between each of the PREMPRO dosage groups and placebo were found at cycles 6, 13, 19, and 26.

Figure 4. ADJUSTED MEAN (SE) PERCENT CHANGE FROM BASELINE AT EACH CYCLE IN SPINE BMD: SUBJECTS COMPLETING IN PREMARIN/MPA GROUPS AND PLACEBO



The bone turnover markers, serum osteocalcin and urinary N-telopeptide, significantly decreased ($p < 0.001$) in all active-treatment groups at cycles 6, 13, 19, and 26 compared with the placebo group. Larger mean decreases from baseline were seen with the active groups than with the placebo group. Significant differences from placebo were seen less frequently in urine calcium; only with PREMPRO 0.625 mg/2.5 mg and 0.45 mg/1.5 mg were there significantly larger mean decreases than with placebo at 3 or more of the 4 time points.

Women's Health Initiative Studies

A substudy of the Women's Health Initiative (WHI) enrolled 16,608 predominantly healthy postmenopausal women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic) to assess the risks and benefits of the use of PREMPRO (0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate per day) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of PREMPRO on menopausal symptoms. The PREMPRO substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." Results are presented in Table 8 below:

Table 8. 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 WARNING, 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.

   The mainstays for decreasing the risk of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500 mg/day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

CONTRAINDICATIONS

Estrogens/progestins combined should not be used in women with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.

2. Known, suspected, or history of cancer of the breast.

3. Known or suspected estrogen-dependent neoplasia.

4. Active deep vein thrombosis, pulmonary embolism or a history of these conditions.

5. Active or recent (e.g., within past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).

6. Liver dysfunction or disease.

7. PREMPRO or PREMPHASE therapy should not be used in patients with known hypersensitivity to their ingredients.

8. Known or suspected pregnancy. There is no indication for PREMPRO or PREMPHASE in pregnancy. There appears to be little or no increased risk of birth defects in women who have used estrogen and progestins from oral contraceptives inadvertently during pregnancy. (See **PRECAUTIONS**.)

WARNINGS
See **BOXED WARNING.**

1. **Cardiovascular disorders.**
Estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogen/progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus should be managed appropriately.

a. Coronary heart disease and stroke. In the PREMPRO substudy of the Women's Health Initiative study (WHI), an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving PREMPRO compared to women receiving placebo (37 vs 30 per 10,000 person-years). The increase in risk was observed in year one and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

In the same substudy of WHI, an increased risk of stroke was observed in women receiving PREMPRO compared to women receiving placebo (29 vs 21 per 10,000 person-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/progestin Replacement Study; HERS) treatment with PREMPRO (0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with PREMPRO did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the PREMPRO-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the PREMPRO group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. Venous thromboembolism (VTE). In the PREMPRO substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving PREMPRO compared to women receiving placebo. The rate of VTE was 34 per 10,000 woman-years in the PREMPRO group compared to 16 per 10,000 woman-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. **Malignant neoplasms.**

a. Breast cancer. Estrogen/progestin therapy in postmenopausal women has been associated with an increased risk of breast cancer. In the PREMPRO substudy of the Women's Health Initiative study, a 26% increase of invasive breast cancer (38 vs 30 per 10,000 woman-years) after an average of 5.2 years of treatment was observed in women receiving PREMPRO compared to women receiving placebo. The increased risk of breast cancer became apparent after 4 years on PREMPRO. The women reporting prior postmenopausal use of estrogen and/or estrogen with progestin had a higher relative risk for breast cancer associated with PREMPRO than those who had never used these hormones. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

Epidemiologic studies have reported an increased risk of breast cancer in association with increasing duration of postmenopausal treatment with estrogens, with or without progestin. This association was reanalyzed in original data from 51 studies that involved treatment with various doses and types of estrogens, with and without progestin. In the reanalysis, an increased risk of having breast cancer diagnosed became apparent after about 5 years of continued treatment, and subsided after treatment had been discontinued for about 5 years. Some later studies have suggested that treatment with estrogen and progestin increases the risk of breast cancer more than treatment with estrogen alone.

A postmenopausal woman without a uterus who requires estrogen should receive estrogen-alone therapy and should not be exposed unnecessarily to progestins. All postmenopausal women should receive yearly breast exams by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age and risk factors.

b. Endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose.

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur at a rate of approximately 1% or less with PREMPRO or PREMPHASE in two large clinical trials. In the two large clinical trials described above, two cases of endometrial cancer were reported to occur among women taking combination Premarin/medroxyprogesterone acetate therapy.

3. **Gallbladder Disease.**
A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

4. **Hypercalcemia.**
Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

5. **Visual Abnormalities.**
Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be discontinued.

PRECAUTIONS

A. General

*1. **Addition of a progestin when a woman has not had a hysterectomy.***
Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared with estrogen-alone regimens. These include a possible increased risk of breast cancer, adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL) and impairment of glucose tolerance.

*2. **Elevated blood pressure.***
In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

*3. **Hypertriglyceridemia.***
In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications. In the HOPE study, the mean percent increase from baseline in serum triglycerides after one year of treatment with PREMPRO 0.625 mg/2.5 mg, 0.45 mg/1.5 mg, and 0.3 mg/1.5 mg compared with placebo were 32.8, 24.8, 23.3, and 10.7, respectively. After two years of treatment, the mean percent changes were 33.0, 17.1, 21.6, and 5.5, respectively.

*4. **Impaired liver function and past history of cholestatic jaundice.***
Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

*5. **Hypothyroidism.***
Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

*6. **Fluid retention.***
Because estrogens/progestins may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

*7. **Hypocalcemia.***
Estrogens should be used with caution in individuals with severe hypocalcemia.

*8. **Ovarian cancer.***
Use of estrogen-only products, in particular for ten or more years, has been associated with an increased risk of ovarian cancer in some epidemiological studies. Other studies did not show a significant association. Data are insufficient to determine whether there is an increased risk with combined estrogen/progestin therapy in postmenopausal women.

*9. **Exacerbation of endometriosis.***
Endometriosis may be exacerbated with administration of estrogens.

*10. **Exacerbation of other conditions.***
Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

B. Patient Information
Physicians are advised to discuss the contents of the PATIENT INFORMATION leaflet with patients for whom they prescribe PREMPRO or PREMPHASE.

C. Laboratory Tests

Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (e.g., estradiol, FSH).

D. Drug/Laboratory Test Interactions

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay), or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.

3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

7. Aminoglutethimide administered concomitantly with medroxyprogesterone acetate (MPA) may significantly depress the bioavailability of MPA.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breasts, uterus, cervix, vagina, testis, and liver. (See **BOXED WARNING, CONTRAINDICATIONS** and **WARNINGS.**)

In a two-year oral study of medroxyprogesterone acetate (MPA) in which female rats were exposed to dosages of up to 5000 mcg/kg/day in their diets (50 times higher – based on AUC values – than the level observed experimentally in women taking 10 mg of MPA), a dose-related increase in pancreatic islet cell tumors (adenomas and carcinomas) occurred. Pancreatic tumor incidence was increased at 1000 and 5000 mcg/kg/day, but not at 200 mcg/kg/day.

A decreased incidence of spontaneous mammary gland tumors was observed in all three MPA-treated groups, compared with controls, in the two-year rat study. The mechanism for the decreased incidence of mammary gland tumors observed in the MPA-treated rats may be linked to the significant decrease in serum prolactin concentration observed in rats.

Beagle dogs treated with MPA developed mammary nodules, some of which were malignant. Although nodules occasionally appeared in control animals, they were intermittent in nature, whereas the nodules in the drug-treated animals were larger, more numerous, persistent, and there were some breast malignancies with metastases. It is known that progestogens stimulate synthesis and release of growth hormone in dogs. The growth hormone, along with the progestogen, stimulates mammary growth and tumors. In contrast, growth hormone in humans is not increased, nor does growth hormone have any significant mammotrophic role. No pancreatic tumors occurred in dogs.

F. Pregnancy
PREMPRO and PREMPHASE should not be used during pregnancy. (See **CONTRAINDICATIONS.**)

G. Nursing Mothers
Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogen and progestin have been identified in the milk of mothers receiving these drugs. Caution should be exercised when PREMPRO or PREMPHASE are administered to a nursing woman.

H. Pediatric Use
PREMPRO and PREMPHASE are not indicated in children.

I. Geriatric Use
Of the total number of subjects in the PREMPRO substudy of the Women's Health Initiative study, 44% (n = 7320) were 65 years and over, while 6.6% (n = 1,095) were 75 and over (see **CLINICAL PHARMACOLOGY, Clinical Studies**). No significant differences in safety were observed between subjects 65 years and over compared to younger subjects. There was a higher incidence of stroke and invasive breast cancer in women 75 and over compared to younger subjects.

With respect to efficacy in the approved indications, there have not been sufficient numbers of geriatric patients involved in studies utilizing Premarin and medroxyprogesterone acetate to determine whether those over 65 years of age differ from younger subjects in their response to PREMPRO or PREMPHASE.

ADVERSE REACTIONS
See **BOXED WARNING, WARNINGS** and **PRECAUTIONS.**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

In a 1-year clinical trial that included 678 postmenopausal women treated with PREMPRO, 351 postmenopausal women treated with PREMPHASE, and 347 postmenopausal women treated with Premarin, the following adverse events occurred at a rate ≥ 5% (see Table 9):

Table 9. ALL TREATMENT EMERGENT STUDY EVENTS REGARDLESS OF DRUG RELATIONSHIP REPORTED AT A FREQUENCY ≥ 5%

	PREMPRO 0.625 mg/2.5 mg continuous (n=340)	PREMPRO 0.625 mg/5.0 mg continuous (n=338)	PREMPHASE 0.625 mg/5.0 mg sequential (n=351)	PREMARIN 0.625 mg daily (n=347)
Body as a whole				
abdominal pain	16%	21%	23%	17%
accidental injury	5%	4%	5%	5%
asthenia	6%	8%	10%	8%
back pain	14%	13%	16%	14%
flu syndrome	10%	13%	12%	14%
headache	36%	28%	37%	38%
infection	16%	16%	18%	14%
pain	11%	13%	12%	13%
pelvic pain	4%	5%	5%	5%
Digestive system				
diarrhea	6%	6%	5%	10%
dyspepsia	6%	6%	5%	5%
flatulence	8%	9%	8%	5%
nausea	11%	9%	11%	11%
Metabolic and Nutritional				
peripheral edema	4%	4%	3%	5%
Musculoskeletal system				
arthralgia	9%	7%	9%	7%
leg cramps	3%	4%	5%	4%
Nervous system				
depression	6%	11%	11%	10%
dizziness	5%	3%	4%	6%
hypertonia	4%	3%	3%	7%
Respiratory system				
pharyngitis	11%	11%	13%	12%
rhinitis	8%	6%	8%	7%
sinusitis	8%	7%	7%	5%
Skin and appendages				
pruritus	10%	8%	5%	4%
rash	4%	6%	4%	3%
Urogenital system				
breast pain	33%	38%	32%	12%
cervix disorder	4%	4%	5%	5%
dysmenorrhea	8%	5%	13%	5%
leukorrhea	6%	5%	9%	8%
vaginal hemorrhage	2%	1%	3%	6%
vaginitis	7%	7%	5%	3%

During the first year of a 2-year clinical trial with 2333 postmenopausal women between 40 and 65 years of age (88% Caucasian), 2001women received continuous regimens of either 0.625 mg of CE with or without 2.5 mg MPA, or 0.45 mg or 0.3 mg of CE with or without 1.5 mg MPA, and 332 received placebo tablets. Table 10 summarizes adverse events that occurred at a rate ≥ 5% in at least 1 treatment group.

TABLE 10. PERCENT OF PATIENTS WITH TREATMENT EMERGENT STUDY EVENTS REGARDLESS OF DRUG RELATIONSHIP REPORTED AT A FREQUENCY ≥ 5% DURING STUDY YEAR 1

Body System Adverse event	Premarin 0.625 mg daily (n = 348)	Prempro 0.625 mg/2.5 mg continuous (n = 331)	Premarin 0.45 mg daily (n = 338)	Prempro 0.45 mg/1.5 mg continuous (n = 331)	Premarin 0.3 mg daily (n = 326)	Prempro 0.3 mg/1.5 mg continuous (n = 327)	Placebo daily (n = 332)
Any adverse event	93%	92%	90%	89%	90%	90%	85%
Body as a whole							
abdominal pain	16%	17%	15%	16%	17%	13%	11%
accidental injury	6%	10%	12%	9%	6%	9%	9%
asthenia	7%	8%	7%	8%	8%	6%	5%
back pain	14%	12%	13%	13%	13%	12%	12%
flu syndrome	11%	8%	11%	11%	10%	10%	11%
headache	26%	28%	32%	29%	29%	33%	28%
infection	18%	21%	22%	19%	23%	18%	22%
pain	17%	14%	18%	15%	20%	20%	18%
Digestive system							
diarrhea	6%	7%	7%	7%	6%	6%	6%
dyspepsia	9%	8%	9%	8%	11%	8%	14%
flatulence	7%	7%	7%	8%	6%	5%	3%
nausea	9%	7%	7%	10%	6%	8%	9%
Musculoskeletal system							
arthralgia	14%	9%	12%	13%	7%	10%	12%
leg cramps	5%	7%	7%	5%	3%	4%	2%
myalgia	5%	5%	5%	5%	9%	4%	8%
Nervous system							
anxiety	5%	4%	4%	5%	4%	2%	4%
depression	7%	11%	8%	5%	5%	8%	7%
dizziness	6%	3%	6%	5%	4%	5%	5%
insomnia	6%	6%	7%	7%	7%	6%	10%
nervousness	3%	3%	5%	2%	2%	2%	2%

TABLE 10. PERCENT OF PATIENTS WITH TREATMENT EMERGENT STUDY EVENTS REGARDLESS OF DRUG RELATIONSHIP REPORTED AT A FREQUENCY ≥ 5% DURING STUDY YEAR 1

Body System Adverse event	Premarin 0.625 mg daily (n = 348)	Prempro 0.625 mg/2.5 mg continuous (n = 331)	Premarin 0.45 mg daily (n = 338)	Prempro 0.45 mg/1.5 mg continuous (n = 331)	Premarin 0.3 mg daily (n = 326)	Prempro 0.3 mg/1.5 mg continuous (n = 327)	Placebo daily (n = 332)
Respiratory system							
cough increased	4%	8%	7%	5%	4%	6%	4%
pharyngitis	10%	11%	10%	8%	12%	9%	11%
rhinitis	6%	8%	9%	9%	10%	10%	13%
sinusitis	6%	8%	11%	8%	7%	10%	7%
upper respiratory infection	12%	10%	10%	9%	9%	11%	11%
Skin and appendages							
pruritus	4%	4%	5%	5%	5%	5%	2%
Urogenital system							
breast enlargement	<1%	5%	1%	3%	2%	2%	<1%
breast pain	11%	26%	12%	21%	7%	13%	9%
dysmenorrhea	4%	5%	3%	6%	1%	3%	<1%
leukorrhea	5%	4%	7%	5%	4%	3%	3%
vaginal hemorrhage	14%	6%	4%	4%	2%	2%	0%
vaginal moniliasis	6%	8%	5%	7%	5%	4%	2%
vaginitis	7%	5%	6%	6%	5%	4%	1%

The following additional adverse reactions have been reported with estrogen and/or progestin therapy:

1. *Genitourinary system*
Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, change in amount of cervical secretion, premenstrual-like syndrome, cystitis-like syndrome, increase in size of uterine leiomyomata, vaginal candidiasis, amenorrhea, changes in cervical erosion, ovarian cancer, endometrial hyperplasia, endometrial cancer.

2. *Breasts*
Tenderness, enlargement, pain, nipple discharge, galactorrhea, fibrocystic breast changes, breast cancer.

3. *Cardiovascular*
Deep and superficial venous thrombosis, pulmonary embolism, thrombophlebitis, myocardial infarction, stroke, increase in blood pressure.

4. *Gastrointestinal*
Nausea, cholestatic jaundice, changes in appetite, vomiting, abdominal cramps, bloating, increased incidence of gallbladder disease, pancreatitis, enlargement of hepatic hemangiomas.

5. *Skin*
Chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, itching, urticaria, pruritus, generalized rash, rash (allergic) with and without pruritus, acne.

6. *Eyes*
Neuro-ocular lesions, e.g., retinal vascular thrombosis and optic neuritis, steepening of corneal curvature, intolerance of contact lenses.

7. *Central Nervous System (CNS)*
Headache, dizziness, mental depression, mood disturbances, anxiety, irritability, nervousness, migraine, chorea, insomnia, somnolence, exacerbation of epilepsy.

8. *Miscellaneous*
Increase or decrease in weight, edema, changes in libido, fatigue, backache, reduced carbohydrate tolerance, aggravation of porphyria, pyrexia, urticaria, angioedema, anaphylactoid/anaphylactic reactions, hypocalcemia, exacerbation of asthma, increased triglycerides.

OVERDOSAGE
Serious ill effects have not been reported following acute ingestion of large doses of estrogen/progestin-containing oral contraceptives by young children. Overdosage of estrogen/progestin may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

Use of estrogens, alone or in combination with a progestin, should be limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as clinically appropriate (e.g., at 3-month to 6-month intervals) to determine if treatment is still necessary (see **BOXED WARNING** and **WARNINGS**). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

PREMPRO therapy consists of a single tablet to be taken once daily.

1. For treatment of moderate to severe vasomotor symptoms and/or 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.

    - PREMPRO 0.3 mg/1.5 mg
    - PREMPRO 0.45 mg/1.5 mg
    - PREMPRO 0.625 mg/2.5 mg
    - PREMPRO 0.625 mg/5 mg
    - PREMPHASE

    Patients should be treated with the lowest effective dose. Generally women should be started at 0.3 mg/1.5 mg PREMPRO daily. Subsequent dosage adjustment may be made based upon the individual patient response. In patients where bleeding or spotting remains a problem, after appropriate evaluation, consideration should be given to changing the dose level. This dose should be periodically reassessed by the healthcare provider.

2. For prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should be considered only for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

    - PREMPRO 0.3 mg/1.5 mg
    - PREMPRO 0.45 mg/1.5 mg
    - PREMPRO 0.625 mg/2.5 mg
    - PREMPRO 0.625 mg/5 mg
    - PREMPHASE

Patients should be treated with the lowest effective dose. Generally women should be started at 0.3 mg/ 1.5 mg PREMPRO daily. Dosage may be adjusted depending on individual clinical and bone mineral density responses. This dose should be periodically reassessed by the healthcare provider.

In patients where bleeding or spotting remains a problem, after appropriate evaluation, consideration should be given to changing the dose level. This dose should be periodically reassessed by the healthcare provider.

PREMPHASE therapy consists of two separate tablets; one maroon 0.625 mg Premarin tablet taken daily on days 1 through 14 and one light-blue tablet, containing 0.625 mg conjugated estrogens and 5 mg of medroxyprogesterone acetate, taken on days 15 through 28.

HOW SUPPLIED
PREMPRO therapy consists of a single tablet to be taken once daily.

PREMPRO 0.3 mg/1.5 mg
Each carton contains 3 EZ DIAL™ dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, cream tablets containing 0.3 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg medroxyprogesterone acetate for oral administration (NDC 0046-0938-09).

PREMPRO 0.45 mg/1.5 mg
Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, gold tablets containing 0.45 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg medroxyprogesterone acetate for oral administration (NDC 0046-0937-09).

PREMPRO 0.625 mg/2.5 mg
Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, peach tablets containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 2.5 mg of medroxyprogesterone acetate for oral administration (NDC 0046-0875-06).

PREMPRO 0.625 mg/5 mg
Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, light-blue tablets containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration (NDC 0046-0975-06).

PREMPHASE therapy consists of two separate tablets; one maroon Premarin tablet taken daily on days 1 through 14 and one light-blue tablet taken on days 15 through 28.

Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 14 oval, maroon Premarin tablets containing 0.625 mg of conjugated estrogens and 14 oval, light-blue tablets that contain 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration (NDC 0046-2573-06).

The appearance of PREMPRO tablets is a trademark of Wyeth Pharmaceuticals.

The appearance of Premarin tablets is a trademark of Wyeth Pharmaceuticals. The appearance of the conjugated estrogens/medroxyprogesterone acetate combination tablets is a registered trademark.

Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

PATIENT INFORMATION
(Updated **DATE HERE**)

PREMPRO™
(conjugated estrogens/medroxyprogesterone acetate tablets)
PREMPHASE®
(conjugated estrogens/medroxyprogesterone acetate tablets)

Read this PATIENT INFORMATION before you start taking PREMPRO or PREMPHASE and read what you get each time you refill PREMPRO or PREMPHASE. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about PREMPRO and PREMPHASE (combinations of estrogens and a progestin)?

Do not use estrogens and progestins to prevent heart disease, heart attacks, or strokes.

Using estrogens and progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots. You and your healthcare provider should talk regularly about whether you still need treatment with PREMPRO or PREMPHASE.

What is PREMPRO or PREMPHASE?

PREMPRO or PREMPHASE are medicines that contain two kinds of hormones, estrogens and a progestin.

PREMPRO or PREMPHASE is used after menopause to:

- **reduce moderate to severe hot flashes.** Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 and 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."

  When the estrogen levels begin dropping, some women get very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild, and they will not need to take estrogens. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether you still need treatment with PREMPRO or PREMPHASE.

- **treat moderate to severe dryness, itching, and burning, in and around the vagina**. You and your healthcare provider should talk regularly about whether you still need treatment with PREMPRO or PREMPHASE to control these problems.

- **help reduce your chances of getting osteoporosis (thin weak bones).** Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use PREMPRO or PREMPHASE only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you. You and your healthcare provider should talk regularly about whether you should continue with PREMPRO or PREMPHASE.

  Weight-bearing exercise, like walking or running, and taking calcium and vitamin D supplements may also lower your chances for getting postmenopausal osteoporosis. It is important to talk about exercise and supplements with your healthcare provider before starting them.

Who should not take PREMPRO or PREMPHASE?

Do not take PREMPRO or PREMPHASE if you have had your uterus removed (hysterectomy).
PREMPRO and PREMPHASE contain a progestin to decrease the chances of getting cancer of the uterus. If you do not have a uterus, you do not need a progestin and you should not take PREMPRO or PREMPHASE.

Do not start taking PREMPRO or PREMPHASE if you:

- **have unusual vaginal bleeding.**
- **currently have or have had certain cancers.**
  Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or had cancer, talk with your healthcare provider about whether you should take PREMPRO or PREMPHASE.
- **had a stroke or heart attack in the past year.**
- **currently have or have had blood clots.**
- **have liver problems.**
- **are allergic to PREMPRO or PREMPHASE or any of their ingredients.** See the end of this leaflet for a list of all the ingredients in PREMPRO and PREMPHASE.
- **think you may be pregnant.**

Tell your healthcare provider:

- **if you are breastfeeding.** The hormones in PREMPRO and PREMPHASE can pass into your milk.

- **about all of your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **about all the medicines you take,** including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how PREMPRO or PREMPHASE works. PREMPRO or PREMPHASE may also affect how your other medicines work.

- **if you are going to have surgery or will be on bedrest.** You may need to stop taking estrogens and progestins.

How Should I Take PREMPRO or PREMPHASE?

- Take one PREMPRO or PREMPHASE tablet at the same time each day.

- If you miss a dose, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your normal schedule. Do not take 2 doses at the same time.

- Estrogens should be used only as long as needed. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about whether you still need treatment with PREMPRO or PREMPHASE.

What are the possible side effects of PREMPRO or PREMPHASE?

Less common but serious side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

Common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps/bloating
- Nausea and vomiting
- Hair loss

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus ("fibroids")
- Vaginal yeast infections
- Mental depression

These are not all the possible side effects of PREMPRO or PREMPHASE. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of getting a serious side effect with PREMPRO or PREMPHASE?

- Talk with your healthcare provider regularly about whether you should continue taking PREMPRO or PREMPHASE.
- See your healthcare provider right away if you get vaginal bleeding while taking PREMPRO or PREMPHASE.
- Have a breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances of getting heart attacks.

General Information about the safe and effective use of PREMPRO and PREMPHASE

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take PREMPRO or PREMPHASE for conditions for which it was not prescribed. Do not give PREMPRO or PREMPHASE to other people, even if they have the same symptoms you have. It may harm them.

Keep PREMPRO and PREMPHASE out of the reach of children.

This leaflet provides a summary of the most important information about PREMPRO and PREMPHASE. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about PREMPRO and PREMPHASE that is written for health professionals. You can get more information by calling the toll free number 800-934-5556.

What are the ingredients in PREMPRO and PREMPHASE?

PREMPRO contains the same conjugated estrogens found in Premarin which are a mixture of sodium estrone sulfate and sodium equilin sulfate and other components including sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol and17β-dihydroequilin. PREMPRO also contains either 1.5, 2.5, or 5 mg of medroxyprogesterone acetate. PREMPRO also contains calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, and yellow ferric oxide or red ferric oxide or FD&C Blue No. 2.

PREMPHASE is two separate tablets. One tablet (maroon color) is 0.625 mg of Premarin which is a mixture of sodium estrone sulfate and sodium equilin sulfate and other components including sodium sulfate conjugates, 17 • •dihydroequilin, 17 • •estradiol and 17 • •dihydroequilin. The maroon tablet also contains calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, stearic acid, sucrose, titanium dioxide, FD&C Blue No. 2, D&C Red No. 27, FD&C Red No. 40. The second tablet (light blue color) contains 0.625 mg of the same ingredients as the maroon color tablet plus 5 mg of medroxyprogesterone acetate. The light blue tablet also contains calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, FD&C Blue No. 2.

PREMPRO therapy consists of a single tablet to be taken once daily.

PREMPRO 0.3 mg/1.5 mg
Each carton includes 3 EZ DIAL™ dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, cream tablets containing 0.3 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg of medroxyprogesterone acetate for oral administration.

PREMPRO 0.45 mg/1.5 mg
Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, gold tablets containing 0.45 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg of medroxyprogesterone acetate for oral administration.

PREMPRO 0.625 mg/2.5 mg
Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, peach tablets containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 2.5 mg of medroxyprogesterone acetate for oral administration.

PREMPRO 0.625 mg/5 mg
Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, light-blue tablets containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration.

PREMPHASE therapy consists of two separate tablets; one maroon Premarin tablet taken daily on days 1 through 14 and one light-blue tablet taken on days 15 through 28.

Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 14 oval, maroon Premarin tablets containing 0.625 mg of conjugated estrogens and 14 oval, light-blue tablets that contain 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration.

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The appearance of Premarin tablets is a trademark of Wyeth Pharmaceuticals. The appearance of the conjugated estrogens/medroxyprogesterone acetate combination tablets is a registered trademark.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-527/S-024, S-026, S-031

MEDICAL REVIEW(S)

Medical Officer's Review

NDA 20-527/S-024, SLR-026, and SLR-031

Date SLR-026 Submitted:	**11/27/02**
Date SLR-031 Submitted:	**2/11/03**
Date S-024 Submitted:	**3/13/03**
Review Completed:	**6/3/03**

Sponsor:	**Wyeth Pharmaceuticals** **P.O. Box 8299** **Philadelphia, PA 19101-8299**
Drug Name:	
Generic:	**Conjugated Estrogens (CE)** **Medroxyprogesterone Acetate (MPA)**
Trade:	**Prempro™**
Pharmacologic category:	**Estrogen**
Dosage Form:	**Oral tablet**
Strengths:	**0.3 mg CE/1.5 mg MPA** **0.45 mg CE/1.5 mg MPA**
Proposed Indication:	**<u>0.3 mg CE/1.5 mg MPA</u>** **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.** **3) Treatment of postmenopausal osteoporosis.** **<u>0.45 mg CE/1.5 mg MPA</u>** **1) Treatment of postmenopausal osteoporosis**
Related Submissions:	**NDA 04-782** **NDA 21-396** **NDA 21-417** **IND 21,696**

Background

Prempro™ is an approved oral drug product that consist of hormones in combination, conjugated estrogens (CE) found in Premarin® Tablets and medroxyprogesterone acetate (MPA), a derivative of progesterone. Three dosage strengths of Prempro™ are currently approved. Prempro™ 0.45/1.5 (0.45 mg CE/1.5 mg MPA), Prempro™ 2.5 (0.625 mg CE/2.5 mg MPA) and Prempro™ 5 (0.625 mg CE/5 mg MPA) are administered orally in a continuous daily regimen.

Premphase® is also an approved drug product containing CE and MPA that is administered orally in a sequential regimen (0.625 mg CE alone administered orally on days 1-14 and 0.625 mg CE/5 mg MPA administered orally on days 15-28 of a 28-day cycle).

Prempro™ 0.45/1.5 is approved 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.

Prempro™ 2.5, Prempro™ 5, and Premphase® are approved for the:

1. Treatment of moderate to severe vasomotor symptoms (VMS) associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) 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 for osteoporosis and non-estrogen medications should be carefully considered.

On December 30, 1994, with the initial approval of Prempro™ 2.5 and Premphase® under NDA 20-303, the Agency requested a Phase 4 commitment to investigate the lowest dose combination of CE/MPA for the prevention of postmenopausal osteoporosis. Two-year, Phase 3 Study 0713D2-309-US was conducted and included 8 treatment groups:

- Three treatment groups of CE alone (0.3 mg, 0.45 mg, and 0.625 mg)
- Four treatment groups of combination CE/MPA (0.3 mg CE/1.5 mg MPA, 0.45 mg CE/1.5 mg MPA, 0.45 mg CE/ 2.5 mg MPA, and 0.625 mg CE/2.5 mg MPA)
- Placebo

On June 15, 2000, two dosage strengths of combined conjugated estrogens/medroxyprogesterone acetate (0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA) were submitted to the Division of Reproductive and Urologic Drug Products (DRUDP) in NDA 20-527/S-017 for the treatment of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. On April 3, 2001, during the review cycle of NDA 20-527/S-017, the Sponsor withdrew, without prejudice, the 0.3 mg CE/1.5 mg MPA dosage strength from consideration.

On April 13, 2001, Prempro™ 0.45 mg CE/1.5 mg MPA received an approvable action from the Agency for the treatment of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. In addition, Prempro™ 0.45 mg CE/1.5 mg MPA demonstrated safety in prevention of endometrial hyperplasia in women with a uterus.

On September 25, 2001, data on the 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA combination dosage strengths in Study 0713D2-309-US was submitted to the Division of Metabolic and Endocrine Drug Products (DMEDP) under NDA 21-396 for the indication for the prevention of postmenopausal osteoporosis.

On November 5, 2001, Prempro™ 0.3 mg CE/1.5 mg MPA dosage strength was resubmitted to DRUDP under NDA 20-527/S-024 for the treatment of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

On April 30, 2002, labeling for the Prempro™ lower dosage strength combinations of CE/MPA (0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA) was submitted to DRUDP under NDA 20-527/SLR-026.

On July 24, 2002, NDA 20-527/SLR-026 labeling for Prempro™ 0.45 mg CE/1.5 mg MPA and Prempro™ 0.3 mg CE/1.5 mg MPA for the prevention of postmenopausal osteoporosis indication received an

approvable action from DRUDP. The Sponsor was advised that before the application could be approved it would be necessary to address the following:

- A number of deficiencies noted during inspection of the Guayama, Puerto Rico and Rouses Point, New York manufacturing facilities; and
- Submit copies of final printed labeling revised as the enclosed labeling for NDA 20-527/S-026. Revisions to the enclosed labeling may be required as a result of ongoing reviews of the findings of the unfavorable benefits to risk profile of Prempro 0.625 mg CE/2.5 mg MPA for primary prevention of coronary heart disease as published by the National Heart Lung and Blood Institute (NHLBI), National Institutes of Health (NIH) for the Women's Health Initiative (WHI) study.

On July 25, 2002, NDA 21-396 for Prempro™ 0.45 mg CE/1.5 mg MPA and Prempro™ 0.3 mg CE/1.5 mg MPA received an approvable action from DMEDP for the prevention of postmenopausal osteoporosis indication. The Sponsor was advised that before the application could be approved it would be necessary to address the following:

- The results of the Women's Health Initiative (WHI) study that were reported in the July 17, 2002 issue of the Journal of the American Medical Association (JAMA). "Please provide an updated risk/benefit analysis of Prempro™ 0.45 mg/1.5 mg and 0.3 mg/1.5 mg ,doses of Prempro™/Premphase® when used in the prevention of postmenopausal osteoporosis."
- "Provide detailed analyses of the cardiovascular adverse event data from the Health and Osteoporosis, Progestin and Estrogen (HOPE) study. To the extent possible, the analysis should parallel those reported in the WHI study."

On August 28, 2002, NDA 20-527/S-024 (Prempro™ 0.3 mg CE/1.5 mg MPA) received an approvable action from DRUDP for the treatment of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. In addition, Prempro™ 0.3 mg CE/1.5 mg MPA demonstrated safety in prevention of endometrial hyperplasia in women with a uterus. The Sponsor was advised that before Prempro™ 0.3 mg CE/1.5 mg MPA could be approved it would be necessary to address the following:

- The Wyeth Laboratories facility in Rouses Point, NY must have a satisfactory cGMP inspection. In addition, all facilities listed in this application must be in cGMP compliance.
- Submit draft labeling identical in content to the enclosed revised labeling NDA 20-527/S-024.
- On July 9, 2002, the National Heart Lung and Blood Institute's (NHLBI) Women's Health Initiative (WHI) published the findings of the unfavorable benefit to risk profile of Prempro (conjugated equine estrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day) for primary prevention of coronary heart disease. The FDA is reviewing these findings and their possible implications for the approved indications, as well as your proposed language, submitted in the "changes being effected" supplement, for NDA 20-527/S-029, to address the WHI results. Revision to the enclosed labeling may be required as a result of these ongoing reviews.

On November 27, 2002, the Sponsor provided a complete response to the DRUDP approvable letter of July 24, 2002 for NDA 20-527/SLR-026 stating the following:

1. **Manufacturing facility** - With regard to the Guayama, Puerto Rico and Rouses Point, New York manufacturing facilities and references in the approvable letter to the deficiencies noted by the inspector, "both facilities were found to be operating in compliance with cGMPs". "No objectionable conditions were found at the Guayama Facility. Objectionable conditions (483 observations) found in Rouses Point were responded to on May 31, 2002; the New York District has reviewed and communicated that the responses and corrective actions were acceptable."
2. **Labeling** – Major points in the proposed draft labeling addressed two subsections: ***Effects on uterine bleeding and spotting***, and ***Effects on bone mineral density***. In addition, "the enclosed proposed labeling for Prempro 0.45 mg/1.5 mg and 0.3 mg/1.5 mg has taken into account the

Division's comments provided in the July 24, 2002 approvable letter as well as includes the proposed language to address the Women's Health Initiative (WHI) results (*Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women, JAMA, July 17, 2002, Vol. 288, No. 3*) and the National Cancer Institute cohort study concerning ovarian cancer (*Menopausal Hormone Replacement Therapy and Risk of Ovarian Cancer, JAMA, July 17, 2002, Vol. 288, No. 3)* submitted in the "changes being effected" supplement for Prempro, NDA 20-527, on August 23, 2002. We acknowledge that further revision may be required as a result of the ongoing reviews of the WHI results."

3. **Safety Profile** – "To satisfy this request, a safety update (November 22, 2002) for conjugated estrogens/medroxyprogesterone acetate is included as Item 9 of this submission, which covers the reporting period of January 1, 2002 – September 30, 2002. There were no additional safety reports for Protocol 0713D2-309-US during this reporting period."

On December 3, 2002, the Sponsor provided a complete response to the DMEDP approvable letter of July 25, 2002 for NDA 21-396 stating the following:

1. **Risk Benefit Analysis** – "As per the Agency's request in the July 25, 2002 approvable letter, taking into account the results of the Women's Health Initiative (WHI) study that were reported in the July 17, issue of JAMA (*Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women, JAMA, July 17, 2002, Vol. 288, No. 3*), we are providing as part of our complete response under Item 9 an updated risk/benefit analysis of the 0.45 mg/1.5 mg and 0.3 mg /1.5 mg doses of Prempro when used for the prevention of postmenopausal osteoporosis."
2. **Analyses of cardiovascular event data from the HOPE study** - "As per the Agency's request in the July 25, 2002 approvable letter of July 25, 2002 for detailed analyses of the cardiovascular event data which parallels the results of the WHI study as reported in the July 17, 2002 issue of JAMA, on November 18, 2002 we submitted our initial review of the cardiovascular adverse event data from the HOPE study."
3. **Chemistry** - With regard to the Guayama, Puerto Rico and Rouses Point, New York manufacturing facilities and references in the approvable letter to the deficiencies noted by the inspector, "both facilities were found to be operating in compliance with cGMPs". "No objectionable conditions were found at the Guayama Facility. Objectionable conditions (483 observations) found in Rouses Point were responded to on May 31, 2002; the New York District has reviewed and communicated that the responses and corrective actions were acceptable."
4. **Safety Profile** – "To satisfy this request, a safety update (November 22, 2002) for conjugated estrogens/medroxyprogesterone acetate is included as Item 9 of this submission, which covers the reporting period of January 1, 2002 – September 30, 2002. There were no additional safety reports for Protocol 0713D2-309-US during this reporting period."

On January 31, 2003, the Investigations and Preapproval Compliance Branch, Office of Compliance advised DRUDP that the Establishment Evaluation System (EES) had been updated to reflect an acceptable GMP status for NDA 20-527 (0.45 mg CE/1.5 mg MPA) and NDA 21-396 (0.3 mg CE/1.5 mg MPA and 0.45 mg CE/1.5 mg MPA).

On February 11, 2003, the Sponsor submitted a Special Supplement – Changes Being Effected (SLR-031, CBE 0) to provide for minor revisions in the text of the **CLINICAL PHARMACOLOGY** section and add safety information to the **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS** sections of labeling. Minor revisions to the test of the **PATIENT INFORMATION** leaflet were also submitted.

On March 13, 2003, the Sponsor provided a complete response to the DRUDP approvable letter of August 28, 2002 for NDA 20-527/S-024 stating the following:

1. **Chemistry** - With regard to the Guayama, Puerto Rico and Rouses Point, New York manufacturing facilities and references in the approvable letter to the deficiencies noted by the inspector, "both facilities were found to be operating in compliance with cGMPs". "No

objectionable conditions were found at the Guayama Facility. Objectionable conditions (483 observations) found in Rouses Point were responded to on May 31, 2002; the New York District has reviewed and communicated that the responses and corrective actions were acceptable."

2. **Labeling** – "The enclosed draft labeling for Prempro 0.3 mg/1.5 mg addresses the Agency's comments provided with the August 28, 2002 approvable letter as well as the comments received at the teleconference on February 6, 2003 between Wyeth and DRUDP to discuss proposed labeling for Prempro 0.45 mg/1.5 mg (NDA 20-527/s-017). The enclosed draft labeling for Prempro 0.3 mg/1.5 mg also has been updated to reflect the labeling approved by the Agency on January 8, 2003 for Prempro marketed product formulations."

On May 2, 2003, an overall acceptable recommendation was issued by the Investigations and Preapproval Compliance Branch, Office of Compliance for NDA 20-527 (0.3 mg CE/1.5 mg MPA).

Chemistry, Manufacturing and Controls

Please see the Chemistry, Manufacturing and Controls Reviews.

Final Labeling

Please see the attached PREMPRO™/PREMPHASE® label.

The proposed labeling submitted on November 27, 2002 and May 29, 2003 for NDA 21-527/SLR-026, February 11, 2003 and May 29, 2003 for NDA 20-527/SLR-031, and March 13, 2003 and May 29, 2003 for NDA 20-527/S-024 was combined and modified in accordance with the Agency's 2003 draft labeling guidance entitled, "Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Prescribing Information for Health Care Providers and Patient Labeling" (see **Federal Register**/ Volume 68/ Monday, February 3, 2003/Notices), and the PREMPRO™/PREMPHASE® approved labeling dated March 12, 2003.

A **BOXED WARNING** was added to the label. Minor revisions have been made to the **CLINICAL PHARMACOLOGY** section under the **Pharmacokinetics** subsections to update the text and Tables 1 and 2.

Revisions have been made to the **Clinical Studies** subsections to update Table 3 under ***Effects on vasomotor symptoms***, Tables 5 and 6 under ***Effects on the endometrium***, Figures 1 and 2 under ***Effects on uterine bleeding or spotting***, and to incorporate the HOPE study findings under *Effects on bone mineral density*.

The (b) (4) subsection has been deleted. A ***Women's Health Initiative Studies*** subsection (text and Table 8) has been added.

Per the Agency's 2003 draft labeling guidance for noncontraceptive estrogen drug products and Supplement-031, the following sections have been revised accordingly: **INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION**.

The **PATIENT INFORMATION** insert has been modified in compliance with the plain language initiative, recommendations from the Division of Drug Marketing, Advertising and Communications (DDMAC) and the Division of Surveillance, Research & Communication Support (DSRCS), and the Agency's 2003 draft labeling guidance for noncontraceptive estrogen drug products.

Conclusions and Recommendations

From a clinical perspective, NDA 20-527/S-024, SLR-026, and SLR-031 can be approved. The Sponsor should submit copies of final printed labeling revised as the enclosed labeling for NDA 20-527/S-024, SLR-026, and SLR-031.

Theresa H. van der Vlugt, MD, M.P.H.
Medical Officer

Attachment

PREMPRO™
(conjugated estrogens/medroxyprogesterone acetate tablets)
PREMPHASE®
(conjugated estrogens/medroxyprogesterone acetate tablets)

℞ **only**

WARNING

Estrogens and progestins should not be used for the prevention of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during 5 years of treatment with conjugated equine estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (see **CLINICAL PHARMACOLOGY, Clinical Studies**). Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

PREMPRO™ 0.3 mg/1.5 mg therapy consists of a single tablet containing 0.3 mg of the conjugated estrogens (CE) found in Premarin® tablets and 1.5 mg of medroxyprogesterone acetate (MPA) for oral administration.

PREMPRO 0.45 mg/1.5 mg therapy consists of a single tablet containing 0.45 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg of medroxyprogesterone acetate for oral administration.

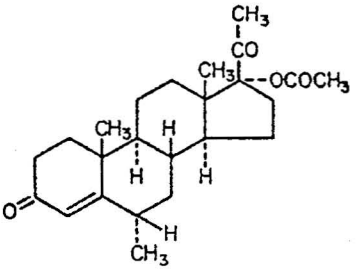
PREMPRO 0.625 mg/2.5 mg therapy consists of a single tablet containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 2.5 mg of medroxyprogesterone acetate for oral administration.

PREMPRO 0.625 mg/5.0 mg therapy consists of a single tablet containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration.

PREMPHASE® therapy consists of two separate tablets, a maroon Premarin tablet containing 0.625 mg of conjugated estrogens that is taken orally on days 1 through 14 and a light-blue tablet containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate that is taken orally on days 15 through 28.

The conjugated equine estrogens found in Premarin tablets are a mixture of sodium estrone sulfate and sodium equilin sulfate. They contain as concomitant components, as sodium sulfate conjugates, 17 α-dihydroequilin, 17 α-estradiol and 17 β-dihydroequilin.

Medroxyprogesterone acetate is a derivative of progesterone. It is a white to off-white, odorless, crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and in dioxane, sparingly soluble in alcohol and in methanol, slightly soluble in ether, and insoluble in water. The chemical name for MPA is pregn-4-ene-3, 20-dione, 17-(acetyloxy)-6-methyl-, (6α)-. Its molecular formula is $C_{24}H_{34}O_4$, with a molecular weight of 386.53. Its structural formula is:



PREMPRO 0.3 mg/1.5 mg

Each cream tablet for oral administration contains 0.3 mg conjugated estrogens, 1.5 mg medroxyprogesterone acetate, and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, yellow ferric oxide.

PREMPRO 0.45 mg/1.5 mg

Each gold tablet for oral administration contains 0.45 mg conjugated estrogens, 1.5 mg medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose,

magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, yellow ferric oxide.

PREMPRO 0.625 mg/2.5 mg
Each peach tablet for oral administration contains 0.625 mg conjugated estrogens, 2.5 mg of medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, red ferric oxide.

PREMPRO 0.625 mg/5 mg
Each light-blue tablet for oral administration contains 0.625 mg conjugated estrogens, 5 mg of medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, FD&C Blue No. 2.

PREMPHASE
Each maroon Premarin tablet for oral administration contains 0.625 mg of conjugated estrogens and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, stearic acid, sucrose, titanium dioxide, FD&C Blue No. 2, D&C Red No. 27, FD&C Red No. 40. These tablets comply with USP Drug Release Test 1.

Each light-blue tablet for oral administration contains 0.625 mg of conjugated estrogens and 5 mg of medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, FD&C Blue No. 2.

CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

Parenterally administered medroxyprogesterone acetate (MPA) inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation, although available data indicate that this does not occur when the usually recommended oral dosage is given as single daily doses. MPA may achieve its beneficial effect on the endometrium in part by decreasing nuclear estrogen receptors and suppression of epithelial DNA synthesis in endometrial tissue. Androgenic and anabolic effects of MPA have been noted, but the drug is apparently devoid of significant estrogenic activity.

Pharmacokinetics

Absorption

Conjugated estrogens are soluble in water and are well absorbed from the gastrointestinal tract after release from the drug formulation. However, PREMPRO and PREMPHASE contain a formulation of medroxyprogesterone acetate (MPA) that is immediately released and conjugated estrogens that are slowly released over several hours. MPA is well absorbed from the gastrointestinal tract. Table 1 summarizes the mean pharmacokinetic parameters for unconjugated and conjugated estrogens, and medroxyprogesterone acetate following administration of 2 PREMPRO 0.625 mg/2.5 mg and 2 PREMPRO 0.625 mg/5 mg tablets to healthy postmenopausal women.

Table 1. PHARMACOKINETIC PARAMETERS FOR UNCONJUGATED AND CONJUGATED ESTROGENS (CE) AND MEDROXYPROGESTERONE ACETATE (MPA)

DRUG	2 x 0.625 mg CE/2.5 mg MPA Combination Tablets (n=54)				2 x 0.625 mg CE/5 mg MPA Combination Tablets (n=51)			
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (pg/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (pg•h/mL)	**C_{max}** (pg/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (pg•h/mL)
Unconjugated Estrogens								
Estrone	175 (23)	7.6 (24)	31.6 (23)	5358 (34)	124 (43)	10 (35)	62.2 (137)	6303 (40)
BA* -Estrone	159 (26)	7.6 (24)	16.9 (34)	3313 (40)	104 (49)	10 (35)	26.0 (100)	3136 (51)
Equilin	71 (31)	5.8 (34)	9.9 (35)	951 (43)	54 (43)	8.9 (34)	15.5 (53)	1179 (56)
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Conjugated Estrogens								
Total Estrone	6.6 (38)	6.1 (28)	20.7 (34)	116 (59)	6.3 (48)	9.1 (29)	23.6 (36)	151 (42)
BA* -Total Estrone	6.4 (39)	6.1 (28)	15.4 (34)	100 (57)	6.2 (48)	9.1 (29)	20.6 (35)	139 (40)
Total Equilin	5.1 (45)	4.6 (35)	11.4 (25)	50 (70)	4.2 (52)	7.0 (36)	17.2 (131)	72 (50)
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Medroxyprogesterone Acetate								
MPA	1.5 (40)	2.8 (54)	37.6 (30)	37 (30)	4.8 (31)	2.4 (50)	46.3 (39)	102 (28)

BA* = Baseline adjusted
C_{max} = peak plasma concentration
t_{max} = time peak concentration occurs
$t_{1/2}$ = apparent terminal-phase disposition half-life ($0.693/\lambda_z$)
AUC = total area under the concentration-time curve

Table 2 summarizes the mean pharmacokinetic parameters for unconjugated and conjugated estrogens and medroxyprogesterone acetate following administration of 2 PREMPRO 0.45 mg/1.5 mg and 2 PREMPRO 0.3 mg/1.5 mg tablets to healthy, postmenopausal women.

Table 2. PHARMACOKINETIC PARAMETERS FOR UNCONJUGATED AND CONJUGATED ESTROGENS (CE) AND MEDROXYPROGESTERONE ACETATE (MPA)

DRUG	2 x 0.3 mg CE/1.5 mg MPA Combination (n = 30)				2 x 0.45 mg CE/1.5 mg MPA Combination (n = 61)			
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (pg/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (pg•h/mL)	**C_{max}** (pg/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (pg•h/mL)
Unconjugated Estrogens								
Estrone	79	9.4	51.3	5029	91	9.8	48.9	5786
	(35)	(86)	(30)	(45)	(30)	(47)	(28)	(42)
BA* -Estrone	56	9.4	19.8	1429	67	9.8	21.5	2042
	(46)	(86)	(39)	(49)	(37)	(47)	(49)	(52)
Equilin	30	7.9	14.0	590	35	8.5	16.4	825
	(43)	(42)	(75)	(42)	(40)	(34)	(49)	(44)
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Conjugated Estrogens								
Total Estrone	2.4	7.1	26.5	62	3.0	8.2	25.9	78
	(38)	(27)	(33)	(48)	(37)	(39)	(23)	(40)
BA* -Total	2.2	7.1	16.3	41	2.8	8.2	16.9	56
Estrone	(36)	(27)	(32)	(44)	(36)	(39)	(36)	(39)
Total Equilin	1.5	5.5	11.5	22	1.9	7.2	12.2	31
	(47)	(29)	(24)	(41)	(42)	(33)	(25)	(52)
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Medroxyprogesterone Acetate								
MPA	1.2	2.8	42.3	29.4	1.2	2.7	47.2	32.0
	(42)	(61)	(34)	(30)	(42)	(52)	(41)	(36)

BA* = Baseline adjusted
C_{max} = peak plasma concentration
t_{max} = time peak concentration occurs
$t_{1/2}$ = apparent terminal-phase disposition half-life ($0.693/\lambda_z$)
AUC = total area under the concentration-time curve

Food-Effect: Single dose studies in healthy, postmenopausal women were conducted to investigate any potential drug interaction when PREMPRO or PREMPHASE is administered with a high fat breakfast. Administration with food decreased the C_{max} of total estrone by 18 to 34% and increased total equilin C_{max} by 38% compared to the fasting state, with no other effect on the rate or extent of absorption of other conjugated or unconjugated estrogens. Administration with food approximately doubles MPA C_{max} and increases MPA AUC by approximately 20 to 30%.

Dose Proportionality: The C_{max} and AUC values for MPA observed in two separate pharmacokinetic studies conducted with 2 PREMPRO 0.625 mg/2.5 mg or 2 PREMPRO or PREMPHASE 0.625 mg/5 mg tablets exhibited nonlinear dose proportionality; doubling the MPA dose from 2 x 2.5 to 2 x 5.0 mg increased the mean C_{max} and AUC by 3.2 and 2.8 folds, respectively.

The dose proportionality of estrogens and medroxyprogesterone acetate was assessed by combining pharmacokinetic data across another two studies totaling 61 healthy, postmenopausal women. Single conjugated estrogens doses of 2 x 0.3 mg, 2 x 0.45 mg, or 2 x 0.625 mg were administered either alone or in combination with medroxyprogesterone acetate doses of 2 x 1.5 mg or 2 x 2.5 mg. Most of the estrogen components demonstrated dose proportionality; however, several estrogen components did not. Medroxyprogesterone acetate pharmacokinetic parameters increased in a dose-proportional manner.

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin. MPA is approximately 90% bound to plasma proteins but does not bind to SHBG.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women a significant proportion of the circulating estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens. Metabolism and elimination of MPA occurs primarily in the liver via hydroxylation, with subsequent conjugation and elimination in the urine.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Most metabolites of MPA are excreted as glucuronide conjugates with only minor amounts excreted as sulfates.

Special Populations

No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

Drug Interactions

Data from a single-dose drug-drug interaction study involving conjugated estrogens and medroxyprogesterone acetate indicate that the pharmacokinetic disposition of both drugs is not altered when the drugs are coadministered. No other clinical drug-drug interaction studies have been conducted with conjugated estrogens.

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Clinical Studies

Effects on vasomotor symptoms

In the first year of the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, a total of 2805 postmenopausal women (average age 53.3 ± 4.9 years) were randomly assigned to one of eight treatment groups of either placebo or conjugated estrogens with or without medroxyprogesterone acetate. Efficacy for vasomotor symptoms was assessed during the first 12 weeks of treatment in a subset of symptomatic women (n = 241) who had at least 7 moderate to severe hot flushes daily or at least 50 moderate to severe hot flushes during the week before randomization. PREMPRO 0.625 mg/2.5 mg, 0.45 mg/1.5 mg, and 0.3 mg/1.5 mg were shown to be statistically better than placebo at weeks 4 and 12 for relief of both the frequency and severity of moderate to severe vasomotor symptoms. Table 3 shows the adjusted mean number of hot flushes in the PREMPRO 0.625 mg/2.5 mg, 0.45 mg/1.5 mg, 0.3 mg /1.5 mg, and placebo groups during the initial 12-week period.

Table 3: SUMMARY TABULATION OF THE NUMBER OF HOT FLUSHES PER DAY – MEAN VALUES AND COMPARISONS BETWEEN THE ACTIVE TREATMENT GROUPS AND THE PLACEBO GROUP – PATIENTS WITH AT LEAST 7 MODERATE TO SEVERE FLUSHES PER DAY OR AT LEAST 50 PER WEEK AT BASELINE, LOCF

Treatment[a] (No. of Patients) Time Period (week)	No. of Hot Flushes/Day Baseline Mean ± SD	Observed Mean ± SD	Mean Change ± SD	p-Values vs. Placebo[b]
0.625 mg/2.5 mg (n = 34)				
4	11.98 ± 3.54	3.19 ± 3.74	-8.78 ± 4.72	<0.001
12	11.98 ± 3.54	1.16 ± 2.22	-10.82 ± 4.61	<0.001
0.45mg/1.5mg (n = 29)				
4	12.61 ± 4.29	3.64 ± 3.61	-8.98 ± 4.74	<0.001
12	12.61 ± 4.29	1.69 ± 3.36	-10.92 ± 4.63	<0.001
0.3 mg/1.5 mg (n = 33)				
4	11.30 ± 3.13	3.70 ± 3.29	-7.60 ± 4.71	<0.001
12	11.30 ± 3.13	1.31 ± 2.82	-10.00 ± 4.60	<0.001
Placebo (n = 28)				
4	11.69 ± 3.87	7.89 ± 5.28	-3.80 ± 4.71	-
12	11.69 ± 3.87	5.71 ± 5.22	-5.98 ± 4.60	-

a: Identified by dosage (mg) of Premarin/MPA or placebo.

b. There were no statistically significant differences between the 0.625 mg/2.5 mg, 0.45 mg/1.5 mg, and 0.3 mg/1.5 mg groups at any time period.

Effects on vulvar and vaginal atrophy

Results of vaginal maturation indexes at cycles 6 and 13 showed that the differences from placebo were statistically significant ($p < 0.001$) for all treatment groups (conjugated estrogens alone and conjugated estrogens/medroxyprogesterone acetate treatment groups).

Effects on the endometrium

In a 1-year clinical trial of 1376 women (average age 54.0 ± 4.6 years) randomized to PREMPRO 0.625 mg/2.5 mg (n=340), PREMPRO 0.625 mg/5 mg (n=338), PREMPHASE 0.625 mg/5 mg (n=351), or Premarin 0.625 mg alone (n=347), results of evaluable biopsies at 12 months (n=279, 274, 277, and 283, respectively) showed a reduced risk of endometrial hyperplasia in the two PREMPRO treatment groups (less than 1%) and in the PREMPHASE treatment group (less than 1%; 1% when focal hyperplasia was included) compared to the Premarin group (8%; 20% when focal hyperplasia was included). See Table 4.

Table 4. INCIDENCE OF ENDOMETRIAL HYPERPLASIA AFTER ONE YEAR OF TREATMENT

	Groups			
	PREMPRO 0.625 mg/2.5 mg	PREMPRO 0.625 mg/5 mg	PREMPHASE 0.625 mg/5 mg	Premarin 0.625 mg
Total number of patients	340	338	351	347
Number of patients with evaluable biopsies	279	274	277	283
No. (%) of patients with biopsies				
• all focal and non-focal hyperplasia	2 (<1)*	0 (0)*	3 (1)*	57 (20)
• excluding focal cystic hyperplasia	2 (<1)*	0 (0)*	1 (<1)*	25 (8)

*Significant ($p < 0.001$) in comparison with Premarin (0.625 mg) alone.

In the first year of the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, 2001 women (average age 53.3 ± 4.9 years) of whom 88% were Caucasian were treated with either Premarin 0.625 mg alone (n = 348), Premarin 0.45 mg alone (n = 338), Premarin 0.3 mg alone (n = 326) or PREMPRO 0.625 mg/2.5 mg (n = 331), PREMPRO 0.45 mg/1.5 mg (n = 331) or PREMPRO 0.3 mg/1.5 mg (n = 327). Results of evaluable endometrial biopsies at 12 months showed a reduced risk of endometrial hyperplasia or cancer in the PREMPRO treatment groups compared with the corresponding Premarin alone treatment groups, except for the PREMPRO 0.3 mg /1.5 mg and Premarin 0.3 mg alone groups, in each of which there was only 1 case. See Table 5.

No endometrial hyperplasia or cancer was noted in those patients treated with the continuous combined regimens who continued for a second year in the osteoporosis and metabolic substudy of the HOPE study. See Table 6.

Table 5. INCIDENCE OF ENDOMETRIAL HYPERPLASIA/CANCER[a] AFTER ONE YEAR OF TREATMENT[b]

	Groups					
Patient	Prempro 0.625 mg/2.5 mg	Premarin 0.625 mg	Prempro 0.45 mg/1.5 mg	Premarin 0.45 mg	Prempro 0.3 mg/1.5 mg	Premarin 0.3 mg
Total number of patients	331	348	331	338	327	326
Number of patients with evaluable biopsies	278	249	272	279	271	269
No. (%) of patients with biopsies						
• hyperplasia/cancer[a] (consensus[c])	0 (0)[d]	20 (8)	1 (< 1)[a,d]	9 (3)	1 (< 1)[e]	1 (<1)[a]

a: All cases of hyperplasia/cancer were endometrial hyperplasia except for 1 patient in the Premarin 0.3 mg group diagnosed with endometrial cancer based on endometrial biopsy, and 1 patient in the Premarin/MPA 0.45 mg/1.5 mg group diagnosed with endometrial cancer based on endometrial biopsy.

b: Two (2) primary pathologists evaluated each endometrial biopsy. Where there was lack of agreement on the presence or absence of hyperplasia/cancer between the two, a third pathologist adjudicated (consensus).

c. For an endometrial biopsy to be counted as consensus endometrial hyperplasia or cancer, at least 2 pathologists had to agree on the diagnosis.

d: Significant ($p < 0.05$) in comparison with corresponding dose of Premarin alone.

e: Non-significant in comparison with corresponding dose of Premarin alone.

TABLE 6. OSTEOPOROSIS AND METABOLIC SUBSTUDY, INCIDENCE OF ENDOMETRIAL HYPERPLASIA/CANCER[a] AFTER TWO YEARS OF TREATMENT[b]

	Groups					
Patient	Prempro 0.625 mg/2.5 mg	Premarin 0.625 mg	Prempro 0.45 mg/1.5 mg	Premarin 0.45 mg	Prempro 0.3 mg/1.5 mg	Premarin 0.3 mg
Total number of patients	75	65	75	74	79	73
Number of patients with evaluable biopsies	62	55	69	67	75	63
No. (%) of patients with biopsies						
• hyperplasia/cancer[a] (consensus[c])	0 (0)[d]	15 (27)	0 (0)[d]	10 (15)	0 (0)[d]	2 (3)

a: All cases of hyperplasia/cancer were endometrial hyperplasia in patients who continued for a second year in the osteoporosis and metabolic substudy of the HOPE study.

b: Two (2) primary pathologists evaluated each endometrial biopsy. Where there was lack of agreement on the presence or absence of hyperplasia/cancer between the two, a third pathologist adjudicated (consensus).

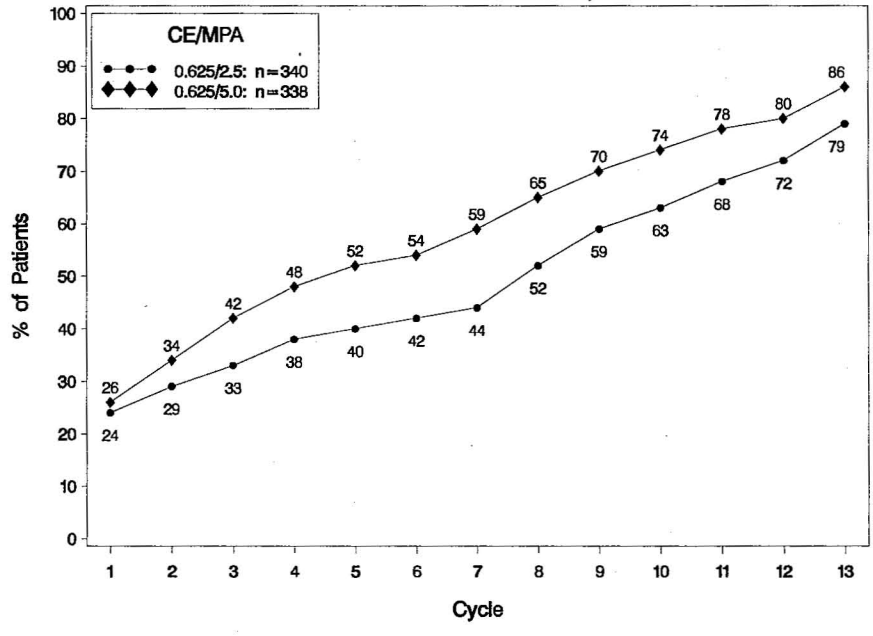
c. For an endometrial biopsy to be counted as consensus endometrial hyperplasia or cancer, at least 2 pathologists had to agree on the diagnosis.

d: Significant ($p < 0.05$) in comparison with corresponding dose of Premarin alone.

Effects on uterine bleeding or spotting

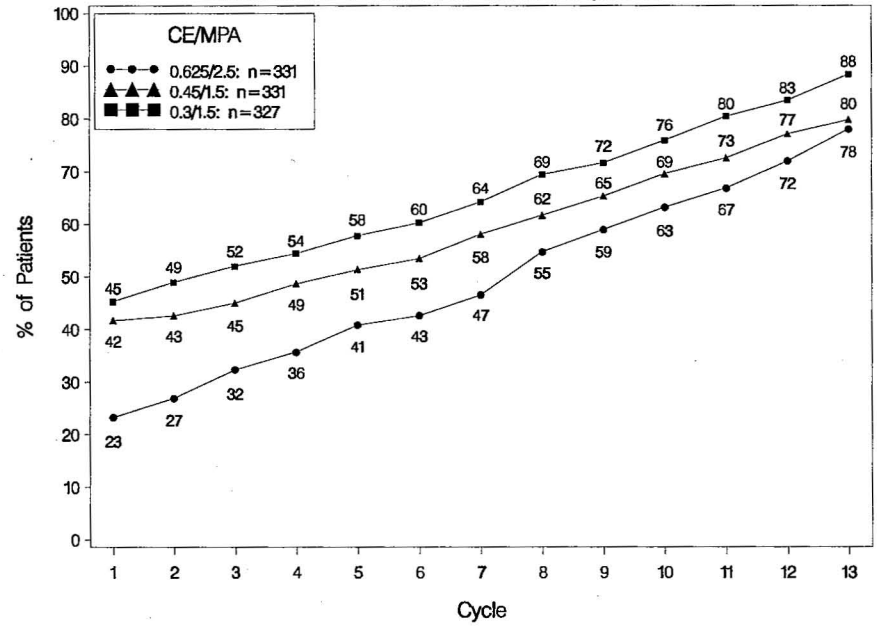
The effects of PREMPRO on uterine bleeding or spotting, as recorded on daily diary cards, were evaluated in 2 clinical trials. Results are shown in Figures 1 and 2.

FIGURE 1. PATIENTS WITH CUMULATIVE AMENORRHEA OVER TIME
PERCENTAGES OF WOMEN WITH NO BLEEDING OR SPOTTING
AT A GIVEN CYCLE THROUGH CYCLE 13
INTENT-TO-TREAT POPULATION, LOCF



Note: The percentage of patients who were amenorrheic in a given cycle and through cycle 13 is shown. If data were missing, the bleeding value from the last reported day was carried forward (LOCF).

FIGURE 2. PATIENTS WITH CUMULATIVE AMENORRHEA OVER TIME
PERCENTAGES OF WOMEN WITH NO BLEEDING OR SPOTTING
AT A GIVEN CYCLE THROUGH CYCLE 13
INTENT-TO-TREAT POPULATION, LOCF



Note: The percentage of patients who were amenorrheic in a given cycle and through cycle 13 is shown. If data were missing, the bleeding value from the last reported day was carried forward (LOCF).

Effects on bone mineral density

Health and Osteoporosis, Progestin and Estrogen (HOPE) Study

The HOPE study was a double-blind, randomized, placebo/active-drug-controlled, multicenter study of healthy postmenopausal women with an intact uterus. Subjects (mean age 53.3 ± 4.9 years) were 2.3 ± 0.9 years, on average, since menopause, and took one 600-mg tablet of elemental calcium (Caltrate) daily. Subjects were not given vitamin D supplements. They were treated with PREMPRO 0.625 mg/2.5 mg, 0.45 mg/1.5 mg or 0.3 mg/1.5 mg, comparable doses of Premarin alone, or placebo. Prevention of bone loss was assessed by measurement of bone mineral density (BMD), primarily at the anteroposterior lumbar spine (L_2 to L_4). Secondarily, BMD measurements of the total body, femoral neck, and trochanter were also analyzed. Serum osteocalcin, urinary calcium, and N-telopeptide were used as bone turnover markers (BTM) at cycles 6, 13, 19, and 26.

Intent-to-treat subjects

All active treatment groups showed significant differences from placebo in each of the 4 BMD endpoints. These significant differences were seen at cycles 6, 13, 19, and 26. With PREMPRO, the mean percent increases in the primary efficacy measure (L_2 to L_4 BMD) at the final on-therapy evaluation (cycle 26 for those who completed and the last

available evaluation for those who discontinued early) were 3.28% with 0.625 mg/2.5 mg, 2.18% with 0.45 mg/1.5 mg, and 1.71% with 0.3 mg/1.5 mg. The placebo group showed a mean percent decrease from baseline at the final evaluation of 2.45%. These results show that the lower dose regimens of PREMPRO were effective in increasing L_2 to L_4 BMD compared with placebo and, therefore, support the efficacy of lower doses of PREMPRO.

The analysis for the other 3 BMD endpoints yielded mean percent changes from baseline in femoral trochanter that were generally larger than those seen for L_2 to L_4 and changes in femoral neck and total body that were generally smaller than those seen for L_2 to L_4. Significant differences between groups indicated that each of the PREMPRO treatment groups was more effective than placebo for all 3 of these additional BMD endpoints. With regard to femoral neck and total body, the continuous combined treatment groups all showed mean percent increases in BMD while the placebo group showed mean percent decreases. For femoral trochanter, each of the PREMPRO groups showed a mean percent increase that was significantly greater than the small increase seen in the placebo group. The percent changes from baseline to final evaluation are shown in Table 7.

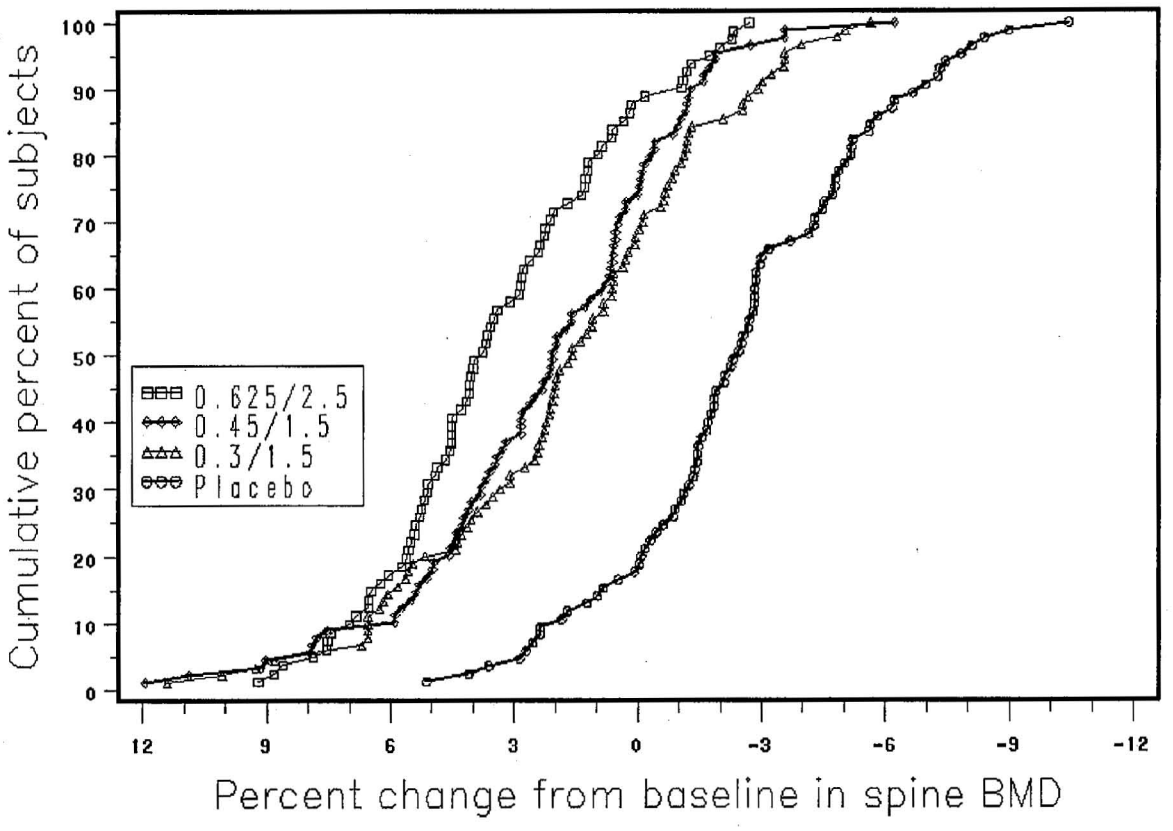
Table 7. PERCENT CHANGE IN BONE MINERAL DENSITY: COMPARISON BETWEEN ACTIVE AND PLACEBO GROUPS IN THE INTENT-TO-TREAT POPULATION, LAST OBSERVATION CARRIED FORWARD

Region Evaluated Treatment Group[a]	No. of Subjects	Baseline (g/cm^2) Mean ± SD	Change from Baseline (%) Adjusted Mean ± SE	p-Value vs Placebo
L_2 to L_4 BMD				
0.625/2.5	81	1.14 ± 0.16	3.28 ± 0.37	<0.001
0.45/1.5	89	1.16 ± 0.14	2.18 ± 0.35	<0.001
0.3/1.5	90	1.14 ± 0.15	1.71 ± 0.35	<0.001
Placebo	85	1.14 ± 0.14	-2.45 ± 0.36	
Total body BMD				
0.625/2.5	81	1.14 ± 0.08	0.87 ± 0.17	<0.001
0.45/1.5	89	1.14 ± 0.07	0.59 ± 0.17	<0.001
0.3/1.5	91	1.13 ± 0.08	0.60 ± 0.16	<0.001
Placebo	85	1.13 ± 0.08	-1.50 ± 0.17	
Femoral neck BMD				
0.625/2.5	81	0.89 ± 0.14	1.62 ± 0.46	<0.001
0.45/1.5	89	0.89 ± 0.12	1.48 ± 0.44	<0.001
0.3/1.5	91	0.86 ± 0.11	1.31 ± 0.43	<0.001
Placebo	85	0.88 ± 0.14	-1.72 ± 0.45	
Femoral trochanter BMD				
0.625/2.5	81	0.77 ± 0.14	3.35 ± 0.59	0.002
0.45/1.5	89	0.76 ± 0.12	2.84 ± 0.57	0.011
0.3/1.5	91	0.76 ± 0.12	3.93 ± 0.56	<0.001
Placebo	85	0.75 ± 0.12	0.81 ± 0.58	

a: Identified by dosage (mg/mg) of Premarin/MPA or placebo.

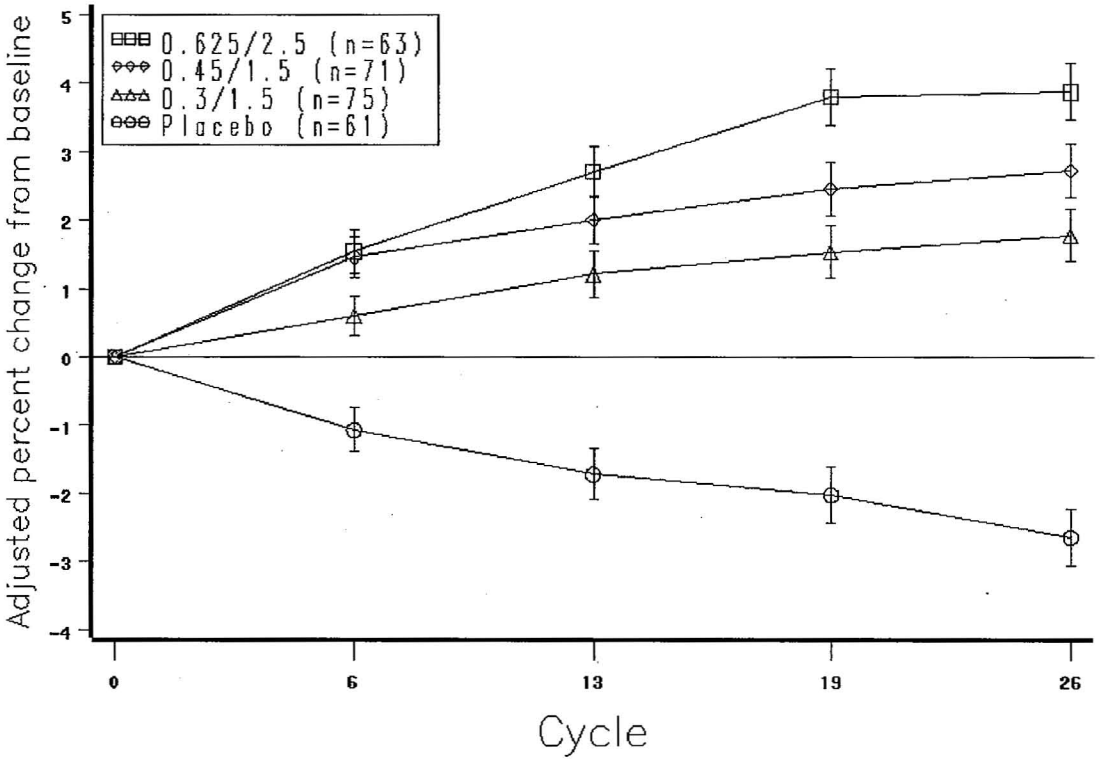
Figure 3 shows the cumulative percentage of subjects with percent changes from baseline in spine BMD equal to or greater than the percent change shown on the x-axis.

Figure 3. CUMULATIVE PERCENT OF SUBJECTS WITH CHANGES FROM BASELINE IN SPINE BMD OF GIVEN MAGNITUDE OR GREATER IN PREMARIN/MPA AND PLACEBO GROUPS



The mean percent changes from baseline in L_2 to L_4 BMD for women who completed the bone density study are shown with standard error bars by treatment group in Figure 4. Significant differences between each of the PREMPRO dosage groups and placebo were found at cycles 6, 13, 19, and 26.

Figure 4. ADJUSTED MEAN (SE) PERCENT CHANGE FROM BASELINE AT EACH CYCLE IN SPINE BMD: SUBJECTS COMPLETING IN PREMARIN/MPA GROUPS AND PLACEBO



The bone turnover markers, serum osteocalcin and urinary N-telopeptide, significantly decreased ($p < 0.001$) in all active-treatment groups at cycles 6, 13, 19, and 26 compared with the placebo group. Larger mean decreases from baseline were seen with the active groups than with the placebo group. Significant differences from placebo were seen less frequently in urine calcium; only with PREMPRO 0.625 mg/2.5 mg and 0.45 mg/1.5 mg were there significantly larger mean decreases than with placebo at 3 or more of the 4 time points.

Women's Health Initiative Studies

A substudy of the Women's Health Initiative (WHI) enrolled 16,608 predominantly healthy postmenopausal women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic) to assess the risks and benefits of the use of PREMPRO (0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate per day) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of PREMPRO on menopausal symptoms. The PREMPRO substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." Results are presented in Table 8 below:

Table 8. 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 WARNING, 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.

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500 mg/day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

CONTRAINDICATIONS
Estrogens/progestins combined should not be used in women with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.

2. Known, suspected, or history of cancer of the breast.

3. Known or suspected estrogen-dependent neoplasia.

4. Active deep vein thrombosis, pulmonary embolism or a history of these conditions.

5. Active or recent (e.g., within past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).

6. Liver dysfunction or disease.

7. PREMPRO or PREMPHASE therapy should not be used in patients with known hypersensitivity to their ingredients.

8. Known or suspected pregnancy. There is no indication for PREMPRO or PREMPHASE in pregnancy. There appears to be little or no increased risk of birth defects in women who have used estrogen and progestins from oral contraceptives inadvertently during pregnancy. (See **PRECAUTIONS**.)

WARNINGS
See **BOXED WARNING.**

1. **Cardiovascular disorders.**
Estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogen/progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus should be managed appropriately.

a. Coronary heart disease and stroke. In the PREMPRO substudy of the Women's Health Initiative study (WHI), an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving PREMPRO compared to women receiving placebo (37 vs 30 per 10,000 person-years). The increase in risk was observed in year one and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

In the same substudy of WHI, an increased risk of stroke was observed in women receiving PREMPRO compared to women receiving placebo (29 vs 21 per 10,000 person-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/progestin Replacement Study; HERS) treatment with PREMPRO (0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with PREMPRO did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the PREMPRO-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the PREMPRO group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. Venous thromboembolism (VTE). In the PREMPRO substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving PREMPRO compared to women receiving placebo. The rate of VTE was 34 per 10,000 woman-years in the PREMPRO group compared to 16 per 10,000 woman-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. **Malignant neoplasms.**

a. Breast cancer. Estrogen/progestin therapy in postmenopausal women has been associated with an increased risk of breast cancer. In the PREMPRO substudy of the Women's Health Initiative study, a 26% increase of invasive breast cancer (38 vs 30 per 10,000 woman-years) after an average of 5.2 years of treatment was observed in women receiving PREMPRO compared to women receiving placebo. The increased risk of breast cancer became apparent after 4 years on PREMPRO. The women reporting prior postmenopausal use of estrogen and/or estrogen with progestin had a higher relative risk for breast cancer associated with PREMPRO than those who had never used these hormones. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

Epidemiologic studies have reported an increased risk of breast cancer in association with increasing duration of postmenopausal treatment with estrogens, with or without progestin. This association was reanalyzed in original data from 51 studies that involved treatment with various doses and types of estrogens, with and without progestin. In the reanalysis, an increased risk of having breast cancer diagnosed became apparent after about 5 years of continued treatment, and subsided after treatment had been discontinued for about 5 years. Some later studies have suggested that treatment with estrogen and progestin increases the risk of breast cancer more than treatment with estrogen alone.

A postmenopausal woman without a uterus who requires estrogen should receive estrogen-alone therapy and should not be exposed unnecessarily to progestins. All postmenopausal women should receive yearly breast exams by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age and risk factors.

b. Endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose.

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur at a rate of approximately 1% or less with PREMPRO or PREMPHASE in two large clinical trials. In the two large clinical trials described above, two cases of endometrial cancer were reported to occur among women taking combination Premarin/medroxyprogesterone acetate therapy.

3. **Gallbladder Disease.**
A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

4. **Hypercalcemia.**
Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

5. **Visual Abnormalities.**
Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be discontinued.

PRECAUTIONS

A. General

1. ***Addition of a progestin when a woman has not had a hysterectomy.***
Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared with estrogen-alone regimens. These include a possible increased risk of breast cancer, adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL) and impairment of glucose tolerance.

2. ***Elevated blood pressure.***
In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

3. ***Hypertriglyceridemia.***
In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with

elevations of plasma triglycerides leading to pancreatitis and other complications. In the HOPE study, the mean percent increase from baseline in serum triglycerides after one year of treatment with PREMPRO 0.625 mg/2.5 mg, 0.45 mg/1.5 mg, and 0.3 mg/1.5 mg compared with placebo were 32.8, 24.8, 23.3, and 10.7, respectively. After two years of treatment, the mean percent changes were 33.0, 17.1, 21.6, and 5.5, respectively.

4. ***Impaired liver function and past history of cholestatic jaundice.***
Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

5. ***Hypothyroidism.***
Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. ***Fluid retention.***
Because estrogens/progestins may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

7. ***Hypocalcemia.***
Estrogens should be used with caution in individuals with severe hypocalcemia.

8. ***Ovarian cancer.***
Use of estrogen-only products, in particular for ten or more years, has been associated with an increased risk of ovarian cancer in some epidemiological studies. Other studies did not show a significant association. Data are insufficient to determine whether there is an increased risk with combined estrogen/progestin therapy in postmenopausal women.

9. ***Exacerbation of endometriosis.***
Endometriosis may be exacerbated with administration of estrogens.

10. ***Exacerbation of other conditions.***
Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

B. Patient Information
Physicians are advised to discuss the contents of the PATIENT INFORMATION leaflet with patients for whom they prescribe PREMPRO or PREMPHASE.

C. Laboratory Tests

Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (e.g., estradiol, FSH).

D. Drug/Laboratory Test Interactions

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay), or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.

3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

7. Aminoglutethimide administered concomitantly with medroxyprogesterone acetate (MPA) may significantly depress the bioavailability of MPA.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breasts, uterus, cervix, vagina, testis, and liver. (See **BOXED WARNING, CONTRAINDICATIONS** and **WARNINGS.**)

In a two-year oral study of medroxyprogesterone acetate (MPA) in which female rats were exposed to dosages of up to 5000 mcg/kg/day in their diets (50 times higher – based on AUC values – than the level observed experimentally in women taking 10 mg of MPA), a dose-related increase in pancreatic islet cell tumors (adenomas and carcinomas) occurred. Pancreatic tumor incidence was increased at 1000 and 5000 mcg/kg/day, but not at 200 mcg/kg/day.

A decreased incidence of spontaneous mammary gland tumors was observed in all three MPA-treated groups, compared with controls, in the two-year rat study. The mechanism for the decreased incidence of mammary gland tumors observed in the MPA-treated rats may be linked to the significant decrease in serum prolactin concentration observed in rats.

Beagle dogs treated with MPA developed mammary nodules, some of which were malignant. Although nodules occasionally appeared in control animals, they were intermittent in nature, whereas the nodules in the drug-treated animals were larger, more numerous, persistent, and there were some breast malignancies with metastases. It is known that progestogens stimulate synthesis and release of growth hormone in dogs. The growth hormone, along with the progestogen, stimulates mammary growth and tumors. In contrast, growth hormone in humans is not increased, nor does growth hormone have any significant mammotrophic role. No pancreatic tumors occurred in dogs.

F. Pregnancy
PREMPRO and PREMPHASE should not be used during pregnancy. (See **CONTRAINDICATIONS**.)

G. Nursing Mothers
Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogen and progestin have been identified in the milk of mothers receiving these drugs. Caution should be exercised when PREMPRO or PREMPHASE are administered to a nursing woman.

H. Pediatric Use
PREMPRO and PREMPHASE are not indicated in children.

I. Geriatric Use
Of the total number of subjects in the PREMPRO substudy of the Women's Health Initiative study, 44% (n = 7320) were 65 years and over, while 6.6% (n = 1,095) were 75 and over (see **CLINICAL PHARMACOLOGY, Clinical Studies**). No significant differences in safety were observed between subjects 65 years and over compared to younger subjects. There was a higher incidence of stroke and invasive breast cancer in women 75 and over compared to younger subjects.

With respect to efficacy in the approved indications, there have not been sufficient numbers of geriatric patients involved in studies utilizing Premarin and medroxyprogesterone acetate to determine whether those over 65 years of age differ from younger subjects in their response to PREMPRO or PREMPHASE.

ADVERSE REACTIONS
See **BOXED WARNING, WARNINGS** and **PRECAUTIONS**.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

In a 1-year clinical trial that included 678 postmenopausal women treated with PREMPRO, 351 postmenopausal women treated with PREMPHASE, and 347 postmenopausal women treated with Premarin, the following adverse events occurred at a rate ≥ 5% (see Table 9):

Table 9. ALL TREATMENT EMERGENT STUDY EVENTS REGARDLESS OF DRUG RELATIONSHIP REPORTED AT A FREQUENCY ≥ 5%

	PREMPRO 0.625 mg/2.5 mg continuous (n=340)	PREMPRO 0.625 mg/5.0 mg continuous (n=338)	PREMPHASE 0.625 mg/5.0 mg sequential (n=351)	PREMARIN 0.625 mg daily (n=347)
Body as a whole				
abdominal pain	16%	21%	23%	17%
accidental injury	5%	4%	5%	5%
asthenia	6%	8%	10%	8%
back pain	14%	13%	16%	14%
flu syndrome	10%	13%	12%	14%
headache	36%	28%	37%	38%
infection	16%	16%	18%	14%
pain	11%	13%	12%	13%
pelvic pain	4%	5%	5%	5%
Digestive system				
diarrhea	6%	6%	5%	10%
dyspepsia	6%	6%	5%	5%
flatulence	8%	9%	8%	5%
nausea	11%	9%	11%	11%
Metabolic and Nutritional				
peripheral edema	4%	4%	3%	5%
Musculoskeletal system				
arthralgia	9%	7%	9%	7%
leg cramps	3%	4%	5%	4%
Nervous system				
depression	6%	11%	11%	10%
dizziness	5%	3%	4%	6%
hypertonia	4%	3%	3%	7%
Respiratory system				
pharyngitis	11%	11%	13%	12%
rhinitis	8%	6%	8%	7%
sinusitis	8%	7%	7%	5%
Skin and appendages				
pruritus	10%	8%	5%	4%
rash	4%	6%	4%	3%
Urogenital system				
breast pain	33%	38%	32%	12%
cervix disorder	4%	4%	5%	5%
dysmenorrhea	8%	5%	13%	5%
leukorrhea	6%	5%	9%	8%
vaginal hemorrhage	2%	1%	3%	6%
vaginitis	7%	7%	5%	3%

During the first year of a 2-year clinical trial with 2333 postmenopausal women between 40 and 65 years of age (88% Caucasian), 2001women received continuous regimens of either 0.625 mg of CE with or without 2.5 mg MPA, or 0.45 mg or 0.3 mg of CE with or without 1.5 mg MPA, and 332 received placebo tablets. Table 10 summarizes adverse events that occurred at a rate ≥ 5% in at least 1 treatment group.

TABLE 10. PERCENT OF PATIENTS WITH TREATMENT EMERGENT STUDY EVENTS REGARDLESS OF DRUG RELATIONSHIP REPORTED AT A FREQUENCY ≥ 5% DURING STUDY YEAR 1

Body System Adverse event	Premarin 0.625 mg daily (n = 348)	Prempro 0.625 mg/2.5 mg continuous (n = 331)	Premarin 0.45 mg daily (n = 338)	Prempro 0.45 mg/1.5 mg continuous (n = 331)	Premarin 0.3 mg daily (n = 326)	Prempro 0.3 mg/1.5 mg continuous (n = 327)	Placebo daily (n = 332)
Any adverse event	93%	92%	90%	89%	90%	90%	85%
Body as a whole							
abdominal pain	16%	17%	15%	16%	17%	13%	11%
accidental injury	6%	10%	12%	9%	6%	9%	9%
asthenia	7%	8%	7%	8%	8%	6%	5%
back pain	14%	12%	13%	13%	13%	12%	12%
flu syndrome	11%	8%	11%	11%	10%	10%	11%
headache	26%	28%	32%	29%	29%	33%	28%
infection	18%	21%	22%	19%	23%	18%	22%
pain	17%	14%	18%	15%	20%	20%	18%
Digestive system							
diarrhea	6%	7%	7%	7%	6%	6%	6%
dyspepsia	9%	8%	9%	8%	11%	8%	14%
flatulence	7%	7%	7%	8%	6%	5%	3%
nausea	9%	7%	7%	10%	6%	8%	9%
Musculoskeletal system							
arthralgia	14%	9%	12%	13%	7%	10%	12%
leg cramps	5%	7%	7%	5%	3%	4%	2%
myalgia	5%	5%	5%	5%	9%	4%	8%
Nervous system							
anxiety	5%	4%	4%	5%	4%	2%	4%
depression	7%	11%	8%	5%	5%	8%	7%
dizziness	6%	3%	6%	5%	4%	5%	5%
insomnia	6%	6%	7%	7%	7%	6%	10%
nervousness	3%	3%	5%	2%	2%	2%	2%

TABLE 10. PERCENT OF PATIENTS WITH TREATMENT EMERGENT STUDY EVENTS REGARDLESS OF DRUG RELATIONSHIP REPORTED AT A FREQUENCY ≥ 5% DURING STUDY YEAR 1

Body System Adverse event	Premarin 0.625 mg daily (n = 348)	Prempro 0.625 mg/2.5 mg continuous (n = 331)	Premarin 0.45 mg daily (n = 338)	Prempro 0.45 mg/1.5 mg continuous (n = 331)	Premarin 0.3 mg daily (n = 326)	Prempro 0.3 mg/1.5 mg continuous (n = 327)	Placebo daily (n = 332)
Respiratory system							
cough increased	4%	8%	7%	5%	4%	6%	4%
pharyngitis	10%	11%	10%	8%	12%	9%	11%
rhinitis	6%	8%	9%	9%	10%	10%	13%
sinusitis	6%	8%	11%	8%	7%	10%	7%
upper respiratory infection	12%	10%	10%	9%	9%	11%	11%
Skin and appendages							
pruritus	4%	4%	5%	5%	5%	5%	2%
Urogenital system							
breast enlargement	<1%	5%	1%	3%	2%	2%	<1%
breast pain	11%	26%	12%	21%	7%	13%	9%
dysmenorrhea	4%	5%	3%	6%	1%	3%	<1%
leukorrhea	5%	4%	7%	5%	4%	3%	3%
vaginal hemorrhage	14%	6%	4%	4%	2%	2%	0%
vaginal moniliasis	6%	8%	5%	7%	5%	4%	2%
vaginitis	7%	5%	6%	6%	5%	4%	1%

The following additional adverse reactions have been reported with estrogen and/or progestin therapy:

1. *Genitourinary system*
Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, change in amount of cervical secretion, premenstrual-like syndrome, cystitis-like syndrome, increase in size of uterine leiomyomata, vaginal candidiasis, amenorrhea, changes in cervical erosion, ovarian cancer, endometrial hyperplasia, endometrial cancer.

2. *Breasts*
Tenderness, enlargement, pain, nipple discharge, galactorrhea, fibrocystic breast changes, breast cancer.

3. *Cardiovascular*
Deep and superficial venous thrombosis, pulmonary embolism, thrombophlebitis, myocardial infarction, stroke, increase in blood pressure.

4. *Gastrointestinal*
Nausea, cholestatic jaundice, changes in appetite, vomiting, abdominal cramps, bloating, increased incidence of gallbladder disease, pancreatitis, enlargement of hepatic hemangiomas.

5. *Skin*
Chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, itching, urticaria, pruritus, generalized rash, rash (allergic) with and without pruritus, acne.

6. *Eyes*
Neuro-ocular lesions, e.g., retinal vascular thrombosis and optic neuritis, steepening of corneal curvature, intolerance of contact lenses.

7. *Central Nervous System (CNS)*
Headache, dizziness, mental depression, mood disturbances, anxiety, irritability, nervousness, migraine, chorea, insomnia, somnolence, exacerbation of epilepsy.

8. *Miscellaneous*
Increase or decrease in weight, edema, changes in libido, fatigue, backache, reduced carbohydrate tolerance, aggravation of porphyria, pyrexia, urticaria, angioedema, anaphylactoid/anaphylactic reactions, hypocalcemia, exacerbation of asthma, increased triglycerides.

OVERDOSAGE
Serious ill effects have not been reported following acute ingestion of large doses of estrogen/progestin-containing oral contraceptives by young children. Overdosage of estrogen/progestin may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

Use of estrogens, alone or in combination with a progestin, should be limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as clinically appropriate (e.g., at 3-month to 6-month intervals) to determine if treatment is still necessary (see **BOXED WARNING** and **WARNINGS**). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

PREMPRO therapy consists of a single tablet to be taken once daily.

1. For treatment of moderate to severe vasomotor symptoms and/or 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.

    - PREMPRO 0.3 mg/1.5 mg
    - PREMPRO 0.45 mg/1.5 mg
    - PREMPRO 0.625 mg/2.5 mg
    - PREMPRO 0.625 mg/5 mg
    - PREMPHASE

    Patients should be treated with the lowest effective dose. Generally women should be started at 0.3 mg/1.5 mg PREMPRO daily. Subsequent dosage adjustment may be made based upon the individual patient response. In patients where bleeding or spotting remains a problem, after appropriate evaluation, consideration should be given to changing the dose level. This dose should be periodically reassessed by the healthcare provider.

2. For prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should be considered only for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

    - PREMPRO 0.3 mg/1.5 mg
    - PREMPRO 0.45 mg/1.5 mg
    - PREMPRO 0.625 mg/2.5 mg
    - PREMPRO 0.625 mg/5 mg
    - PREMPHASE

Patients should be treated with the lowest effective dose. Generally women should be started at 0.3 mg/ 1.5 mg PREMPRO daily. Dosage may be adjusted depending on individual clinical and bone mineral density responses. This dose should be periodically reassessed by the healthcare provider.

In patients where bleeding or spotting remains a problem, after appropriate evaluation, consideration should be given to changing the dose level. This dose should be periodically reassessed by the healthcare provider.

PREMPHASE therapy consists of two separate tablets; one maroon 0.625 mg Premarin tablet taken daily on days 1 through 14 and one light-blue tablet, containing 0.625 mg conjugated estrogens and 5 mg of medroxyprogesterone acetate, taken on days 15 through 28.

HOW SUPPLIED
PREMPRO therapy consists of a single tablet to be taken once daily.

PREMPRO 0.3 mg/1.5 mg
Each carton contains 3 EZ DIAL™ dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, cream tablets containing 0.3 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg medroxyprogesterone acetate for oral administration (NDC 0046-0938-09).

PREMPRO 0.45 mg/1.5 mg
Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, gold tablets containing 0.45 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg medroxyprogesterone acetate for oral administration (NDC 0046-0937-09).

PREMPRO 0.625 mg/2.5 mg
Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, peach tablets containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 2.5 mg of medroxyprogesterone acetate for oral administration (NDC 0046-0875-06).

PREMPRO 0.625 mg/5 mg
Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, light-blue tablets containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration (NDC 0046-0975-06).

PREMPHASE therapy consists of two separate tablets; one maroon Premarin tablet taken daily on days 1 through 14 and one light-blue tablet taken on days 15 through 28.

Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 14 oval, maroon Premarin tablets containing 0.625 mg of conjugated estrogens and 14 oval, light-blue tablets that contain 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration (NDC 0046-2573-06).

The appearance of PREMPRO tablets is a trademark of Wyeth Pharmaceuticals.

The appearance of Premarin tablets is a trademark of Wyeth Pharmaceuticals. The appearance of the conjugated estrogens/medroxyprogesterone acetate combination tablets is a registered trademark.

Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

PATIENT INFORMATION
(Updated **DATE HERE**)

PREMPRO™
(conjugated estrogens/medroxyprogesterone acetate tablets)
PREMPHASE®
(conjugated estrogens/medroxyprogesterone acetate tablets)

Read this PATIENT INFORMATION before you start taking PREMPRO or PREMPHASE and read what you get each time you refill PREMPRO or PREMPHASE. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about PREMPRO and PREMPHASE (combinations of estrogens and a progestin)?

Do not use estrogens and progestins to prevent heart disease, heart attacks, or strokes.

Using estrogens and progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots. You and your healthcare provider should talk regularly about whether you still need treatment with PREMPRO or PREMPHASE.

What is PREMPRO or PREMPHASE?

PREMPRO or PREMPHASE are medicines that contain two kinds of hormones, estrogens and a progestin.

PREMPRO or PREMPHASE is used after menopause to:

- **reduce moderate to severe hot flashes.** Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 and 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."

  When the estrogen levels begin dropping, some women get very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild, and they will not need to take estrogens. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether you still need treatment with PREMPRO or PREMPHASE.

- **treat moderate to severe dryness, itching, and burning, in and around the vagina**. You and your healthcare provider should talk regularly about whether you still need treatment with PREMPRO or PREMPHASE to control these problems.

- **help reduce your chances of getting osteoporosis (thin weak bones).** Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use PREMPRO or PREMPHASE only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you. You and your healthcare provider should talk regularly about whether you should continue with PREMPRO or PREMPHASE.

  Weight-bearing exercise, like walking or running, and taking calcium and vitamin D supplements may also lower your chances for getting postmenopausal osteoporosis. It is important to talk about exercise and supplements with your healthcare provider before starting them.

Who should not take PREMPRO or PREMPHASE?

Do not take PREMPRO or PREMPHASE if you have had your uterus removed (hysterectomy).
PREMPRO and PREMPHASE contain a progestin to decrease the chances of getting cancer of the uterus. If you do not have a uterus, you do not need a progestin and you should not take PREMPRO or PREMPHASE.

Do not start taking PREMPRO or PREMPHASE if you:

- **have unusual vaginal bleeding.**
- **currently have or have had certain cancers.**
  Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or had cancer, talk with your healthcare provider about whether you should take PREMPRO or PREMPHASE.
- **had a stroke or heart attack in the past year.**
- **currently have or have had blood clots.**
- **have liver problems.**
- **are allergic to PREMPRO or PREMPHASE or any of their ingredients.** See the end of this leaflet for a list of all the ingredients in PREMPRO and PREMPHASE.
- **think you may be pregnant.**

Tell your healthcare provider:

- **if you are breastfeeding.** The hormones in PREMPRO and PREMPHASE can pass into your milk.

- **about all of your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **about all the medicines you take,** including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how PREMPRO or PREMPHASE works. PREMPRO or PREMPHASE may also affect how your other medicines work.

- **if you are going to have surgery or will be on bedrest.** You may need to stop taking estrogens and progestins.

How Should I Take PREMPRO or PREMPHASE?

- Take one PREMPRO or PREMPHASE tablet at the same time each day.

- If you miss a dose, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your normal schedule. Do not take 2 doses at the same time.

- Estrogens should be used only as long as needed. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about whether you still need treatment with PREMPRO or PREMPHASE.

What are the possible side effects of PREMPRO or PREMPHASE?

Less common but serious side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

Common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps/bloating
- Nausea and vomiting
- Hair loss

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus ("fibroids")
- Vaginal yeast infections
- Mental depression

These are not all the possible side effects of PREMPRO or PREMPHASE. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of getting a serious side effect with PREMPRO or PREMPHASE?

- Talk with your healthcare provider regularly about whether you should continue taking PREMPRO or PREMPHASE.
- See your healthcare provider right away if you get vaginal bleeding while taking PREMPRO or PREMPHASE.
- Have a breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances of getting heart attacks.

General Information about the safe and effective use of PREMPRO and PREMPHASE

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take PREMPRO or PREMPHASE for conditions for which it was not prescribed. Do not give PREMPRO or PREMPHASE to other people, even if they have the same symptoms you have. It may harm them.

Keep PREMPRO and PREMPHASE out of the reach of children.

This leaflet provides a summary of the most important information about PREMPRO and PREMPHASE. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about PREMPRO and PREMPHASE that is written for health professionals. You can get more information by calling the toll free number 800-934-5556.

What are the ingredients in PREMPRO and PREMPHASE?

PREMPRO contains the same conjugated estrogens found in Premarin which are a mixture of sodium estrone sulfate and sodium equilin sulfate and other components including sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol and17β-dihydroequilin. PREMPRO also contains either 1.5, 2.5, or 5 mg of medroxyprogesterone acetate. PREMPRO also contains calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, and yellow ferric oxide or red ferric oxide or FD&C Blue No. 2.

PREMPHASE is two separate tablets. One tablet (maroon color) is 0.625 mg of Premarin which is a mixture of sodium estrone sulfate and sodium equilin sulfate and other components including sodium sulfate conjugates, 17 α-dihydroequilin, 17 α-estradiol and 17 β-dihydroequilin. The maroon tablet also contains calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, stearic acid, sucrose, titanium dioxide, FD&C Blue No. 2, D&C Red No. 27, FD&C Red No. 40. The second tablet (light blue color) contains 0.625 mg of the same ingredients as the maroon color tablet plus 5 mg of medroxyprogesterone acetate. The light blue tablet also contains calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, FD&C Blue No. 2.

PREMPRO therapy consists of a single tablet to be taken once daily.

PREMPRO 0.3 mg/1.5 mg
Each carton includes 3 EZ DIAL™ dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, cream tablets containing 0.3 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg of medroxyprogesterone acetate for oral administration.

PREMPRO 0.45 mg/1.5 mg
Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, gold tablets containing 0.45 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg of medroxyprogesterone acetate for oral administration.

PREMPRO 0.625 mg/2.5 mg
Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, peach tablets containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 2.5 mg of medroxyprogesterone acetate for oral administration.

PREMPRO 0.625 mg/5 mg
Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, light-blue tablets containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration.

PREMPHASE therapy consists of two separate tablets; one maroon Premarin tablet taken daily on days 1 through 14 and one light-blue tablet taken on days 15 through 28.

Each carton includes 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 14 oval, maroon Premarin tablets containing 0.625 mg of conjugated estrogens and 14 oval, light-blue tablets that contain 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration.

The appearance of PREMPRO tablets is a trademark of Wyeth Pharmaceuticals.

The appearance of Premarin tablets is a trademark of Wyeth Pharmaceuticals. The appearance of the conjugated estrogens/medroxyprogesterone acetate combination tablets is a registered trademark.

Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

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/s/

Theresa Van Der Vlugt
6/4/03 04:19:31 PM
MEDICAL OFFICER

Shelley Slaughter
6/4/03 04:43:15 PM
MEDICAL OFFICER
I concur.

NDA 20-527/S-024

Date NDA Submitted:	**11/5/01**
Date NDA Received:	**11/7/01**
Review Completed:	**6/20/02**
Review Finalized:	**8/22/02**

Medical Officer's Review
(Original Review)

Sponsor:	**Wyeth-Ayerst Research** **P.O. Box 8299** **Philadelphia, PA 19101-8299**
Drug Name:	
Generic:	**Conjugated Estrogens (CE)** **Medroxyprogesterone Acetate (MPA)**
Trade:	**Prempro™**
Pharmacologic category:	**Estrogen**
Dosage Form:	**Oral tablet**
Strength:	**0.3 mg CE/1.5 mg MPA**
Proposed Indications:	**1) Treatment of moderate-to-severe vasomotor symptoms associated with the menopause.** **2) Treatment of vulvar and vaginal atrophy associated with the menopause.**
Related Submission:	**IND 21,696**

TABLE OF CONTENTS

SECTION and TOPIC		PAGE
The Executive Summary of the Primary Clinical Review		4
1. RECOMMENDATION		4
1.1.	Recommendations on Approvability	4
1.2.	Recommendations on Postmarketing Studies and/or Risk Management Steps Where Appropriate	4
2. SUMMARY OF CLINICAL FINDINGS		4
2.1.	Brief Overview of the Clinical Program	4
2.2.	Efficacy	5
2.3.	Safety	7
2.4.	Dosing, Regimen, and Administration	9
2.5.	Drug-Drug Interactions	10
2.6.	Special Populations	10
Clinical Review		11
1. INTRODUCTION AND BACKGROUND		11
1.1.	Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication (s), Dose, Regimen, Age Groups	11
1.2.	State of Armamentarium for Indication(s)	11
1.3.	Important Milestones in Product Development	12
1.4.	Other Relevant Information	14
1.5.	Important Issues with Pharmacologically Related Agents	14
2. SIGNIFICANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, AND/OR MICROBIOLOGY		14
2.1.	Chemistry, Manufacturing and Controls	14
2.2.	Animal Pharmacology and Toxicology	14
2.3.	Microbiology	14
3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS		14
3.1.	Pharmacokinetics	14
3.2.	Pharmacodynamics	15
4. DESCRIPTION OF CLINICAL DATA AND SOURCES		15
4.1.	Source of Clinical Data	15
4.2.	Overview of Clinical Trials	16
4.3.	Postmarketing Experience	17
4.4.	Literature Review	17
5. CLINICAL REVIEW METHODS		17
5.1.	Describe How Review was Conducted	17
5.2.	Overview of Materials Consulted in Review	18

5.3. Overview of Methods Used to Evaluate Data Quality and Integrity 18
5.4. Were Trials Conducted in Accordance with Accepted Ethical Standards 18
5.5. Evaluation of Financial Disclosure 18

6. INTEGRATED REVIEW OF EFFICACY 18

6.1. Brief Statement of Conclusions 18
6.2. General Approach to Review of the Efficacy of the Drug 18
6.3. Detailed Review of Trials by Indication 19
6.4. Efficacy Conclusions 30

7. INTEGRATED REVIEW OF SAFETY 31

7.1. Brief Statement of Conclusions 31
7.2. Materials Utilized in the Review 31
7.3. Description of Patient Exposure 31
7.4. Safety Findings from Clinical Studies 32
7.5. Miscellaneous Studies 42
7.6. Literature Review for Safety 42
7.7. Postmarketing Surveillance – If Applicable 42
7.8. Safety Update 43
4-Month Safety Update 43
7.9. Drug Withdrawal, Abuse, and Overdose Experience 43
7.10. Adequacy of Safety Testing 43
7.11. Labeling Safety Issues and Postmarketing Commitments 44

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES 44

9. USE IN SPECIAL POPULATIONS 44

9.1. Evaluation of Applicant's Efficacy and Safety Analyses of Effects of Gender, Age, Race, or Ethnicity. Comment on Adequacy of Applicant's Analyses. 44
9.2. Pediatric Program (e.g., pediatric waivers, deferrals, written requests) 44
9.3. Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy. 44

10. CONCLUSIONS AND RECOMMENDATIONS, AND LABELING 44

10.1. Conclusions Regarding Safety and Efficacy 45
10.2. Recommendations on Approvability 45
10.3. Labeling 45

The Executive Summary of the Primary Clinical Review

1. RECOMMENDATION

1.1. Recommendations on Approvability

The reviewer recommends approval of Prempro™ 0.3 mg conjugated estrogens (CE)/1.5 mg medroxyprogesterone acetate (MPA), henceforth in this review, referred to as 0.3 mg CE/1.5 mg MPA or Prempro™ 0.3 /1.5. The data presented in this supplemental new drug application provides sufficient evidence from one large, controlled clinical trial to support the safety and efficacy of Prempro™ 0.3/1.5 for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause in women with a uterus, and protection of the endometrium from equivalent estrogen-induced endometrial hyperplasia.

1.2. Recommendations on Postmarketing Studies and/or Risk Management Steps Where Appropriate

No postmarketing studies and/or risk management steps are recommended.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief Overview of the Clinical Program

Prempro™ is an approved oral drug product that consist of hormones in combination, conjugated estrogens (CE) found in Premarin® Tablets and medroxyprogesterone acetate (MPA), a derivative of progesterone. Two dosage strengths of Prempro™ are currently approved. Prempro™ 2.5 (0.625 mg CE/2.5 mg MPA) and Prempro™ 5 (0.625 mg CE/5 mg MPA) are administered orally in a continuous daily regimen.

Premphase® is also an approved drug product containing CE and MPA that is administered orally in a sequential regimen (CE alone administered orally on days 1-14 and CE/MPA administered orally on days 15-28 of a 28-day cycle).

Prempro™ 2.5, Prempro™ 5, and Premphase® are approved for the:

1. Treatment of moderate-to-severe vasomotor symptoms (VMS) associated with the menopause.
2. Treatment of vulvar and vaginal atrophy (VVA) associated with the menopause.
3. Prevention of postmenopausal osteoporosis.

On December 30, 1994, with the initial approval of Prempro™ and Premphase® under NDA 20-303, the Agency requested a Phase 4 commitment to investigate the lowest dose combination of CE/MPA for the prevention of postmenopausal osteoporosis.

Two dosage strengths of combined conjugated estrogens/medroxyprogesterone acetate (0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA) were submitted to the Agency on June 15, 2000 in NDA 20-527/S-017 for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause. On April 3, 2001, during the review cycle of NDA 20-527/S-017, the Sponsor withdrew, without prejudice, the 0.3 mg CE/1.5 mg MPA dosage strength from consideration.

On April 13, 2001, Prempro™ 0.45 mg CE/1.5 mg MPA received an Approvable action from the Agency. The Sponsor was advised that before the application could be approved it would be necessary to address the following:

- A number of deficiencies noted during inspection of the Guayama, Puerto Rico manufacturing facility; and
- Submit copies of final printed labeling revised as the enclosed labeling for NDA 20-527/S-017.

In addition, the Sponsor agreed to conduct, as a Phase 4 commitment, an MPA dissolution study and provide to the Agency within four months of approval of supplemental NDA 20-527/S-017 a copy or a summary of the new analytical method for the MPA component of the 0.45 mg CE/1.5 mg MPA combination tablet and the preliminary dissolution data from the study.

Combined 0.3 mg CE/1.5 mg MPA, the dosage strength that is the subject of this supplemental NDA, was investigated in a single, controlled clinical trial to satisfy the post-approval Phase 4 commitment under NDA 20-303. Study 0713D2-309-US was a double-blind, placebo/active drug-controlled clinical trial that randomized 2,805 postmenopausal women between 40 to 65 years of age to one of 8 treatment groups for a 2 year duration of treatment. Phase 3 Study 0713D2-309-US entitled, Health and Osteoporosis, Progestin and Estrogen (HOPE) was designed to investigate the lowest dose combination of CE/MPA for the prevention of postmenopausal osteoporosis.

Study 0713D2-309-US was comprised of two parts: 1) a 1-year basic study with a total of 2,673 postmenopausal women (including 749 subjects assigned to the osteoporosis and metabolic substudy group), and 2) a 2-year osteoporosis and metabolic substudy with 749 postmenopausal women.

At the completion of study year 1 of Study 0713D2-309-US, data on a total of 2,673 treated subjects was analyzed regarding the relief of vasomotor symptoms and vulvar and vaginal atrophy, and protection of the endometrium. The data from study year 1 was presented in NDA 20-527/S-017. No data regarding the prevention of postmenopausal osteoporosis was presented in Supplement-017 as year 2 of the osteoporosis and metabolic substudy of Study 0713D2-309-US was ongoing at the time of the submission on June 15, 2000. The data for the osteoporosis and metabolic substudy from study years 1 and 2 is presented in this submission.

2.2. Efficacy

Overall, the data presented in this submission shows that the 0.3 mg CE/1.5 mg MPA dosage strength is effective in relieving moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause, and protection of the endometrium in generally healthy postmenopausal women between 40 and 65 years of age.

The HOPE study investigated 8 treatment groups as summarized below:

Group (N)	CE (mg)	CE/MPA (mg)
A (348)	0.625	Placebo
B (331)	Placebo	0.625/2.5
C (338)	0.45	Placebo
D (340)	Placebo	0.45/2.5
E (331)	Placebo	0.45/1.5
F (326)	0.3	Placebo
G (327)	Placebo	0.3/1.5
H (332)	Placebo	Placebo

Data analyzed for the VMS indication (number and severity of hot flushes) was obtained from daily diaries completed by 2,673 treated subjects over a 12-week period. However, only a limited subset of treated subjects met the inclusion criteria for a VMS indication.

For a VMS indication, the 1995 Hormone Replacement Therapy (HRT) Guidance for Industry indicates that enrolled subjects should have a minimum of 7 to 8 moderate-to-severe hot flushes per day or 50 to 60 per week at baseline. In the HOPE study, a total of 241 subjects (9% of the 2,673 treated subjects) presented with 7 to 8 moderate-to-severe hot flushes per day at baseline (or an

average of 50 per week) and are included in the VMS subset. These 241 subjects were equally divided between the 8 treatment groups (range between 27 to 34 subjects per group).

Based on the VMS subset data collected over the initial 12 weeks of the HOPE study (number and severity of hot flushes were recorded daily), the 0.3 mg CE/1.5 mg MPA dosage strength was effective in reducing both the number and severity of moderate-to-severe hot flushes at weeks 4 and 12, the primary efficacy time points for a VMS indication ($p<0.001$ versus placebo at both time points). The analysis of vasomotor symptoms at weeks 4 and 12 was considered a final analysis for the basic study population for a VMS indication.

Vaginal Maturation Index results (obtained from vaginal cytology smears collected at baseline, cycle 6 and cycle 13) in year 1 of the HOPE study demonstrate a statistically significant estrogenic effect on vulvar and vaginal tissue for the 0.3 mg CE/1.5 mg MPA dosage strength. The Maturation Index represents the proportion of vaginal superficial cells relative to the number of parabasal and intermediate cells. The percentage of vaginal superficial cells increased significantly from baseline values at cycles 6 and 13 ($p<0.001$ at both time points). A corresponding statistically significant decrease in the percentage of vaginal parabasal cells was likewise demonstrated at cycles 6 and 13 ($p<0.001$ at both time points). The analysis of the Maturation Index at the 1-year time point was considered a final analysis for the basic study population for a VVA indication.

The efficacy of the 0.3 mg CE/1.5 mg MPA dosage strength for protection of the endometrium was also evaluated in Study 0713D2-309-US. Endometrial biopsies were obtained at baseline and twice during study year 1 (between cycles 5-7 and between cycles 12-14). A total of 2,153 evaluable subjects (80%, 2,153 of 2,673 subjects) had a baseline endometrial biopsy, had taken at least one dose of study medication, and had an endometrial biopsy performed between cycles 5-7 and cycles 12-14 or were diagnosed with endometrial hyperplasia or cancer at any time during study year 1. A total of 518 substudy subjects (69%, 518 of 749 subjects) were included in the evaluable population at cycle 26 (had a valid biopsy taken during cycles 25 to 27). Two hundred thirty-one (231; 31%) subjects were excluded in year 2 because they had no valid biopsy taken during cycles 25 to 27 and no endometrial hyperplasia was diagnosed before cycle 25.

The Sponsor's analysis of the HOPE study showed no endometrial cancer occurring during study years 1 and 2. However, two "endometrial malignancies" were recorded in NDA 20-527/S-017 in study year 1. Subject 30924-0011, in the 0.3 mg CE alone group, had an endometrial biopsy reading (scheduled biopsy at cycle 6) of endometrial adenocarcinoma by one primary pathologist during the trial, and a reading of complex hyperplasia with atypia by the other primary pathologist. The third, arbiter, pathologist was not consulted per protocol. Instead, the subject was referred to a private gynecologic oncologist who reviewed the study biopsy slides and recorded a diagnosis of severely atypical endometrial hyperplasia. Subject 30912-0049, in the 0.45 mg CE/1.5 mg MPA treatment group, also had a biopsy reading (scheduled biopsy at cycle 6) of endometrial malignancy during the trial. In this case, one primary pathologist and the arbiter pathologist agreed with a diagnosis of endometrial adenocarcinoma in a polyp. Following a repeat endometrial biopsy, primary pathologists 1 and 2 agreed with a diagnosis of complex hyperplasia with atypia in a polyp. The Sponsor classified both of these subjects as endometrial hyperplasia. A total of 32 cases of endometrial hyperplasia were reported across the 8 treatment groups in study year 1 of the HOPE study.

However, in the proposed revision of the 1995 HRT Guidance, the reading and classification of endometrial biopsy slides relies on a majority decision diagnosis (2 of 3 pathologists) or a worst-case scenario diagnosis (if the three pathologists disagree). Because the third adjudicating pathologist was not consulted for Subject 30924-0011 (which is in violation of the protocol-specified procedures), the clinical review team (the reviewer, a second medical officer [also a board-certified pathologist], and the team leader) followed the most conservative approach and reclassified this case as endometrial adenocarcinoma. If the most conservative approach (worst-case scenario) is not taken, then the diagnosis by majority decision (2 of 3 pathologists) would be accepted. However, atypical hyperplasia is the most pathologically worrisome form of hyperplasia and is considered to be the true precursor of endometrial cancer. For Subject 30912-0049, the clinical review team reclassified this case as

endometrial adenocarcinoma in a polyp based on the majority diagnosis of two of the three study pathologists. Subject 30924-0011 and Subject 30912-0049 were both reclassified as endometrial adenocarcinoma in the Medical Officer's Review of NDA 20-527/S-017. However, the occurrence of one case of endometrial adenocarcinoma in the 0.3 mg CE alone treatment group and one case of endometrial adenocarcinoma in the 0.45 mg CE/1.5 mg MPA treatment group in NDA 20-527/S-017 is no higher than that seen in other large, prospective controlled trials. Although the occurrence of endometrial adenocarcinoma is a rare event, zero to one case of endometrial adenocarcinoma has been reported in either estrogen-alone or estrogen/progestin treatment groups for other large, controlled HRT clinical trials.

Data on the remaining 30 cases of endometrial hyperplasia reported in study year 1 of the HOPE study shows that the rate of endometrial hyperplasia with the 0.625 mg CE alone dosage strength was 8.03% (n = 249, one-sided 95% CI of 0, 11.5), 3.23% with the 0.45 mg CE alone dosage strength (n = 279, one-sided 95% CI of 1, 5.6), and 0.00% with the 0.3 mg CE alone dosage strength. In comparison, the rate of endometrial hyperplasia with the combination 0.625 mg CE/2.5 mg MPA dosage strength and the 0.45 mg CE/1.5 mg MPA dosage strength was 0.00% (n = 278, one-sided 95% CI of 0, 1.1, and n= 272, one-sided 95% CI of 0, 1.2, respectively) while the rate of endometrial hyperplasia with the 0.3 mg CE/1.5 mg MPA dosage strength was 0.37% (n = 272, one-sided 95% CI of 0, 1.8) in study year 1. However, when endometrial hyperplasia or cancer is combined, the 0.3 mg CE/1.5 mg MPA dosage strength demonstrated the same rate of endometrial hyperplasia or cancer compared with the 0.3 mg CE alone dosage strength, 0.37% for both, well within the range of 0% and 1% expected for untreated women.

Per the proposed revision of the 1995 HRT Guidance, for combination drug products intended to demonstrate endometrial safety, the results of a clinical trial should demonstrate a hyperplasia rate that is less than or equal to 1% with an upper bound of a one-sided 95% confidence interval for that rate which does not exceed 4% at one year. Results from year 1 of Study 0713D2-309-US show an incidence of 0.37% for the combined endometrial hyperplasia or cancer rate for the 0.3 mg CE/1.5 mg MPA dosage strength, and the upper bound of a one-sided 95% confidence interval of 0, 1.8, well below the one-sided 95% confidence interval upper bound of 4%.

Twenty-seven (27) cases of endometrial hyperplasia were reported across the 8 treatment groups in study year 2 for the osteoporosis and metabolic substudy population. Results of the analysis of cycle 26 shows no reported cases of endometrial hyperplasia in any of the four combination treatment groups (0.625 mg CE/2.5 mg MPA, 0.45 mg CE/2.5 mg MPA, 0.625 mg CE/1.5 mg MPA, and 0.3 mg CE/1.5 mg MPA). Endometrial hyperplasia occurred only in the CE alone treatment groups. The rate of endometrial hyperplasia with the 0.625 mg CE alone dosage strength was 27% (15 of 55 evaluable subjects), the 0.45 mg CE alone dosage strength was 15% (10 of 67 evaluable subjects), and 3% for the 0.3 mg CE alone dosage strength (2 of 63 evaluable subjects).

In the submitted year 1 study results, the rate of cumulative amenorrhea (percentage of subjects per treatment group with no bleeding or spotting at a given month through month 12) increased with each consecutive cycle. At cycle 13, the 0.3 mg CE/1.5 mg MPA dosage strength demonstrated an improved cumulative amenorrhea rate over the approved Prempro™ 2.5 (0.625 mg CE/2.5 mg MPA). Cumulative amenorrhea rates of 67.6% and 62.2%, respectively, were reported.

2.3. Safety

Higher doses of CE (0.625 mg) and MPA (2.5 mg and 5 mg) have been used in combination HRT tablets since 1994.

The postmenopausal use of estrogen/progestin combinations has been associated with an increased risk of breast cancer, cardiovascular events (myocardial infarction and stroke), venous thromboembolic events (deep vein thrombosis and pulmonary embolism), and gallbladder disease. Please see the Agency's 1992 Guidance for Industry entitled, "Labeling Guidance for Non-Contraceptive Estrogen Drug Products – Prescribing Information for Health Care Providers, and Patient Labeling" and the

draft revision of the 1992 Guidance (**Federal Register**, Vol. 64, No. 186/Monday, September 27, 1999/Notices) for these and other labeled risks associated with the use of estrogen and estrogen/progestin drug products (see the **WARNINGS** and **PRECAUTIONS** sections). Please see the **CONTRAINDICATIONS** section for conditions for which estrogens and estrogen/progestin drug products should not be used. Revision of the Estrogen Class Labeling Guidance is ongoing.

Two recent published reports of controlled clinical trials have presented additional safety information for 0.625 mg CE/2.5 mg MPA (Prempro™ 2.5). Data from the Heart and Estrogen/progestin Replacement Study (HERS and HERS II), a controlled clinical trial of secondary prevention of 2,763 postmenopausal women with established coronary disease, showed that treatment for 6.8 years with 0.625 mg CE/2.5 mg MPA versus placebo in older women (average age of 67 years) with established coronary disease did not reduce the overall rate of coronary heart disease events, and increased rates of venous thromboembolism and biliary tract surgery.[1,2]

A subset of the Women's Health Initiative (WHI), a controlled primary prevention clinical trial of 16,608 primarily healthy postmenopausal women who received 0.625 mg CE/2.5 mg MPA versus placebo was stopped early (after an average of 5.2 years of a planned 8.5 years duration) because overall health risks exceeded benefits.[3] The reported absolute excess risks per 10,000 person-years attributable to 0.625 mg CE/2.5 mg MPA were 8 more cases of invasive breast cancers, 7 more coronary heart disease events, 8 more strokes, and 8 more cases of pulmonary embolism. The increased risk of breast cancer became apparent after 4 years of treatment. The increased risk of coronary heart disease was observed in year one and persisted. The increased risk of stroke was observed in year 2 and persisted. The increased risks of pulmonary embolism was observed during the first year and persisted. The reported absolute risk reductions per 10,000 person-years attributable to 0.625 mg CE/2,5 mg MPA in the WHI were 6 fewer cases of colorectal cancers and 5 fewer hip fractures. The WHI clinical trial did not address the risks and benefits of estrogen/progestin given for the treatment of menopausal symptoms.

In Study 0713D2-309-US in this submission, the treatment emergent adverse event profile of the 0.3 mg CE/1.5 mg MPA dosage strength is similar to that of the currently approved products, Prempro™ 2.5, Prempro™ 5, and Premphase®.

Safety evaluations and monitoring in the submitted study were adequate and complete for the 2,673 total treated subjects in year one (basic study group) and the 749 subjects (osteoporosis and metabolic substudy) in year 2. Two deaths from lung cancer were reported during the conduct of the first year of the HOPE study (Subject 30921-0018 treated with 0.3 mg CE for 134 days and Subject 30937-0129 treated with 0.45 mg CE/2.5 mg MPA for 217 days). Both of these deaths were considered to be unrelated to the use of study medication

Serious adverse events reported during the 2 years of the HOPE study include 4 cases of arterial thrombosis (1 myocardial infarction, 2 strokes, and 1 transient ischemic attack), 3 venous thromboembolic events (2 deep vein thrombosis and 1 pulmonary embolism), seven cases of cholelithiasis with cholecystectomy, and 12 cases of breast cancer (8 cases of breast cancer reported in year 1 and 4 cases of breast cancer reported in year 2).

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[1] Grady D, Herrington D, Bittner V, et al, for the HERS Research Group. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA 2002 Jul 3;288(1):47-57.

[2] Hulley S, Furberg C, Barrett-Connor E, Cauley J, Grady D, et.al., Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA 2002 Jul 3;288(1):58-66

[3] Writing Group for the Women's Health Initiative Investigators. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women, Principal Results From The Women's Health Initiative Randomized Controlled Trial. JAMA 2002 July 17;288(3):321-333.

Of the 8 cases of breast cancer reported in year 1 of the HOPE study, 7 occurred during treatment and one case was diagnosed approximately 12 months after completion of study medication. One case each of breast cancer was reported in the following four treatment groups: 0.625 mg CE alone, 0.625 mg CE/2.5 mg MPA, 0.45 mg CE/1.5 mg MPA, and placebo. The 4 remaining cases of breast cancer occurred in the 0.3 mg CE/1.5 mg MPA treatment group. No cases of breast cancer were reported for the 0.45 mg CE alone, 0.45 mg CE/2.5 mg MPA, and 0.3 mg CE alone treatment groups in year 1.

In year 2 of the osteoporosis and metabolic substudy, a total of 4 cases of breast cancer were reported. Three cases occurred during treatment and one case was diagnosed approximately 9 months post-study. One case of breast cancer was reported in each of the four following treatment groups in year 2 of the substudy: 0.45 mg CE alone, 0.45 mg CE/1.5 mg MPA, 0.3 mg CE alone, and placebo. No cases of breast cancer were reported for the 0.625 mg CE alone, 0.625 mg CE/2.5 mg MPA, 0.45 mg CE/2.5 mg MPA, and 0.3 mg CE/1.5 mg MPA treatment groups.

In summary, of the 12 cases of breast cancer reported during the conduct of the 2-year HOPE study, 7 occurred during treatment in year 1, 3 occurred during treatment in year 2, and 2 were reported post-study. The placebo treatment group (2 cases of breast cancer), all three CE alone treatment groups (1 case of breast cancer each, total of 3), and 3 of the 4 combination CE/MPA treatment groups reported breast cancer (a total of 7 cases of breast cancer). In the combination CE/MPA treatment groups, one case of breast cancer occurred in the 0.625 mg CE/2.5 mg MPA treatment group, two cases of breast cancer occurred in the 0.45 mg CE/1.5 mg MPA treatment group, and 4 cases of breast cancer occurred in the 0.3 mg CE/1.5 mg MPA treatment group (all reported in year 1). Only the 0.45 mg CE/2.5 mg MPA treatment group was free of reported breast cancer.

As noted above, breast cancer, cardiovascular disease, thromboembolic events and cholelithiasis with cholecystectomy are known to occur with estrogen alone and estrogen/progestin combination drug products and, overall, the incidence of these events in the HOPE study correlate with the findings in other large HRT clinical trials of similar treatment duration. However, the known risk for these adverse events, apparent from clinical trials of estrogen alone and estrogen/progestin combination drug products including the results of the Women's Health Initiative, warrant close post-marketing clinical surveillance.

All active-treatment groups, including the 0.3 mg CE/1.5 mg MPA treatment group, showed favorable increases in HDL-cholesterol and HDL_2-cholesterol as opposed to the small changes seen in the placebo treatment group. All active-treatment groups showed favorable decreases in LDL-cholesterol at most or all cycles (statistically significant difference between the 0.3 mg CE/1.5 mg MPA group and placebo at all cycles), while the placebo treatment group showed significant increases at cycles 13, 19, and 26. Overall, these findings show a favorable lipid profile for the 0.3 mg CE/1.5 mg MPA treatment dosage strength.

2.4. Dosing, Regimen, and Administration

Conjugated estrogens tablets are approved for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause. Conjugated estrogens vaginal cream is approved for the treatment of vulvar and vaginal atrophy. Conjugated estrogens intravenous injection is approved for the treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology.

The literature supports the use of low dosage strengths of estrogen to relieve vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause, and the prevention of postmenopausal osteoporosis. To date, oral estrogen dosage strengths approved for the treatment of VMS, VVA, and the prevention of postmenopausal osteoporosis range from 0.5 mg/day to 2.5 mg/day. For transdermal patch systems, dosage strengths range from 0.025 mg/day to 0.1 mg/day.

Because the use of unopposed estrogen in women with a uterus is known to increase the incidence of endometrial hyperplasia (endometrial hyperplasia may be a precursor to endometrial cancer), several

combination estrogen/progestin drug product formulations are approved for the treatment of VMS and VVA (Prempro®, Premphase®, Activella™, femhrt™, Ortho-Prefest™ and Combipatch™).

2.5. Drug-Drug Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects. This information will be provided in labeling.

2.6. Special Populations

Combination CE/MPA is only indicated for use in postmenopausal women with a uterus. Conversely, combination CE/MPA is not intended for use in a pediatric population.

The 0.3 mg CE/1.5 mg MPA dosage strength was not studied in women with liver disease, and estrogens/progestins are contraindicated in postmenopausal women with liver dysfunction or disease. No studies were conducted in women with renal impairment in this submission. Prempro™ is contraindicated in pregnancy.

In a subgroup analysis by age across all 8 treatment groups in year 1 (<50, 50 to 59, ≥ 60 years), the percentages of women with endometrial hyperplasia increased with age: 0.45% (2 cases in 446 subjects), 1.37% (20 cases in 1,454 subjects), and 3.56% (9 cases in 253 subjects), respectively. Twenty-nine of the 30 cases of endometrial hyperplasia that were reported in year 1 occurred in CE alone treatment groups. Only one case of endometrial hyperplasia occurred in the 0.3 mg CE/1.5 mg MPA treatment group in year 1.

Postmenopausal women aged 50 to 59 and ≥ 60 years of age demonstrated a dose-dependent CE alone effect on the endometrium in year 1. The hyperplasia rates in these two age groups were higher with the highest CE alone dose (0.625 mg) and lower with the lowest CE alone dose (0.3 mg). This dose dependent effect was most evident in the group of women ≥ 60 years of age: 22.2% (0.625 mg), 6.25% (0.45 mg), and 2.86% (0.3 mg). However, all three corresponding CE/MPA combination dosage strengths had endometrial hyperplasia rates of zero in women ≥ 60 years of age.

No subgroup analysis by age group was presented in this submission.

Although a subgroup analysis was performed for ethnic origin for year 1, the numbers for the non-white study populations are too small to draw any conclusions. Eighty-eight percent of the study population was white.

Clinical Review

1. INTRODUCTION AND BACKGROUND

1.1. Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication (s), Dose, Regimen, Age Groups

Prempro™ 0.3 mg conjugated estrogens (CE)/1.5 mg medroxyprogesterone acetate (MPA), henceforth in this review, referred to as 0.3 mg CE/1.5 mg MPA or Prempro™ 0.3 /1.5, consist of two hormones, conjugated estrogens found in Premarin® tablets and medroxyprogesterone acetate, a derivative of progesterone. The proposed indications for Prempro™ 0.3 /1.5 mg are:

- The treatment of moderate-to-severe vasomotor symptoms associated with the menopause.
- The treatment of vulvar and vaginal atrophy associated with the menopause.

The Sponsor also proposes to demonstrate that this low dose CE/MPA combination protects the endometrium by reducing the incidence of estrogen-induced endometrial hyperplasia.

Prempro™ 0.3/1.5 is a lower dosage strength of the CE/MPA combination tablets that are currently approved for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause, and the prevention of osteoporosis in postmenopausal women with an intact uterus:

- Prempro™ 2.5 (0.625 mg CE/2.5 mg MPA), daily continuous oral administration
- Prempro™ 5 (0.625 mg CE/5 mg MPA), daily continuous oral administration
- Premphase® (0.625 mg CE/5 mg MPA), daily continuous oral administration of one tablet of 0.625 mg CE on days 1-14 followed by the oral administration of one single tablet of 0.625 mg CE/5 mg MPA on days 15-28 of a 28-day cycle.

1.2. State of Armamentarium for Indication(s)

The 1995 Hormone Replacement Therapy (HRT) Guidance entitled, "Guidance for Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products Used for Hormone Replacement Therapy in Postmenopausal Women", and the proposed revision of the 1995 HRT Guidance for Industry, recommends that products intended to treat moderate-to-severe vasomotor symptoms (VMS) should show both a clinically and a statistically significant reduction in the frequency and severity of hot flushes in the treated groups compared to the control groups. This reduction in the frequency and severity of hot flushes should occur within 4 weeks of initiation of treatment and should be maintained throughout 12 weeks of treatment. Subjective measures (i.e., patient daily diaries) are used as primary efficacy endpoints.

For products intended to treat vulvar and vaginal atrophy (VVA), vaginal cytology smears are collected pre-treatment and at week 12 (end-of-study) to determine the percentages of parabasal, intermediate and superficial cells (Maturation Index). In 1999, the Division incorporated two additional efficacy variables for this indication: 1) the assessment of vaginal pH (along with other physician assessment of signs) and, 2) the patient self-assessment of symptoms at baseline and at end-of-study. The physician assessment of signs includes the following categories: vaginal pH, color of the vaginal epithelium, and vaginal mucosal integrity (friability and petechiae). The subject's self-assessment of vaginal symptoms includes the following categories: vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, vaginal pain associated with sexual activity, and vaginal bleeding associated with sexual activity. Three primary efficacy variables are considered for a treatment of vulvar and vaginal atrophy indication:

- The change in the Maturation Index between baseline and week 12 (statistically significant decrease of parabasal vaginal cells and increase in superficial vaginal cells).

- The change in vaginal pH between baseline and week 12 (statistically significant lowering of vaginal pH).
- The change in the subject self-assessment of symptoms between baseline and week 12. The primary efficacy analysis should show statistically significant improvement in the moderate-to-severe symptom identified by the subject as the most bothersome.

1.3. Important Milestones in Product Development

Premarin® (conjugated estrogens) was approved in 1942 for the relief of vasomotor symptoms. In 1972, the Federal Register Drug Efficacy Study Implementation Notice (DESI 1543, 37 FR 14826 dated July 31, 1972), which was based on the National Academy of Sciences-National Research Council Drug Efficacy Study Group (NAS-NRC) review of published literature, found non-contraceptive estrogen drugs (including Premarin®) effective for several "DESI Indications". This 1972 notice and two additional notices (DESI 1543, 41 FR 43114 dated September 29, 1976 and 51 FR 12568 dated April 11, 1986) defined these "DESI Indications" as follows: moderate-to-severe vasomotor symptoms (MSVS) associated with the menopause, senile vaginitis, kraurosis vulvae, pruritis vulvae, abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, female hypogonadism, amenorrhea, female castration, primary ovarian failure, prevention of postpartum breast engorgement, palliation of selected cases of inoperable progressing mammary and prostatic carcinoma, and postmenopausal osteoporosis.

On September 29, 1976, Federal Register notice 41 FR 43108 instituted so-called "class labeling" for estrogen products, e.g., uniform labeling on aspects of benefits and risks.

In 1991, the Fertility and Maternal Health Drugs Advisory Committee (FMHD/AC) concluded that the addition of a progestin to estrogen replacement therapy for more than 10 days per cycle reduces endometrial cancer risk without reducing estrogen's protective effect on bone density.

On December 30, 1994, the FDA approved NDA 20-303 for Premarin® (0.625 mg CE) plus Cycrin® brand of MPA (2.5 mg and 5 mg MPA) in women with intact uteri for the treatment of vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause, and the prevention of postmenopausal osteoporosis. NDA 20-303, for Prempro™ and Premphase® was approved with a commitment for a Phase 4 study to investigate the effectiveness of lower doses of Prempro™ on bone mineral density and endometrial endpoints. The Phase 4 study protocol (Study 0713D2-309-US) was designed in accordance with the March 20, 1995 HRT Guidance and the November 19, 1997 Committee for Proprietary Medicinal Products (CPMP), "Points to Consider on Hormone Replacement Therapy (CPMP/EWP/021/97) publication. The trial length, use of washout periods, inclusion criteria, measurements of hot flushes and endometrial hyperplasia endpoints were conducted as recommended in these documents.

Initially, Prempro™ and Premphase® were co-packaged as one tablet of CE and one tablet of MPA. The Prempro™ regimen involved taking one tablet of 0.625 mg CE and one tablet of 2.5 mg MPA daily (two tablets total). The Premphase® regimen involved taking one tablet of 0.625 mg CE daily for 14 days followed by one tablet of 0.625 mg CE and one tablet of 5 mg MPA (two tablets total) daily for days 15-28 of a 28-day cycle. However, on November 17, 1995, the FDA approved NDA 20-527 for CE/MPA as a single combination tablet (conjugated estrogens tablet (b) (4) containing MPA). Following the approval of a single combination tablet, the Prempro™ 2.5 regimen consists of the daily continuous oral administration of one single tablet of 0.625 mg CE/2.5 mg MPA. The Premphase® regimen consists of the daily continuous oral administration of one tablet of 0.625 mg CE on days 1-14 followed by the oral administration of one single tablet of 0.625 mg CE/2.5 mg MPA on days 15-28 of a 28-day cycle.

On January 9, 1998, NDA 20-527/S-006 was approved for Prempro™ 5. The Prempro™ 5 regimen consists of the daily continuous administration of a one single tablet of 0.625 mg CE/5 mg MPA. Prempro™ 5 is also approved for the treatment of moderate-to-severe vasomotor symptoms and vulvar

and vaginal atrophy associated with the menopause, and the prevention of osteoporosis in postmenopausal women with an intact uterus.

In NDA 20-527/S-017, dated June 15, 2000, two lower dosage strengths of conjugated estrogens/medroxyprogesterone acetate (0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA) were submitted to the Agency for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause, and for protection of the endometrium. On April 3, 2001, during the review cycle of NDA 20-527/S-017, the Sponsor withdrew, without prejudice, the 0.3 mg CE/1.5 mg MPA dosage strength from consideration.

On April 13, 2001, Prempro™ 0.45 mg CE/1.5 mg MPA received an Approvable action from the Agency for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause. In addition, Prempro™ 0.45 mg CE/1.5 mg MPA demonstrated safety in prevention of endometrial hyperplasia in women with a uterus. The Sponsor was advised that before the application could be approved it would be necessary to address the following:

- A number of deficiencies noted during inspection of the Guayama, Puerto Rico manufacturing facility; and
- Submit copies of final printed labeling revised as the enclosed labeling for NDA 20-527/S-017.

As previously stated, Study 0713D2-309-US was undertaken to satisfy a post-approval commitment to the Agency to determine the lowest effective dose of CE/MPA for the prevention of postmenopausal osteoporosis in women with a uterus. The 1995 HRT Guidance specifies a comparison of three doses of CE/MPA to evaluate postmenopausal osteoporosis prevention, as well as a comparison of unopposed CE treatments to evaluate endometrial protection. In the proposed revision of the 1995 HRT Guidance, to demonstrate protection of the endometrium for estrogen/progestin drug products, clinical trials should include at least two progestin dosage strengths for each estrogen dosage strength studied, one of the progestin doses should be a non-effective dose. A comparison estrogen-alone treatment group is no longer recommended.

The CE/MPA combinations used in Study 0713D2-309-US were 0.625 mg/2.5 mg, 0.45 mg/2.5 mg, 0.45 mg/1.5 mg, and 0.3 mg/1.5 mg. Matching doses of unopposed CE of 0.625 mg. 0.45 mg, and 0.3 mg were also used. The 2.5 mg MPA dose was used because it is currently the lowest approved dose to reduce the incidence of endometrial hyperplasia in women with a uterus receiving 0.625 mg CE alone. The 1.5 mg MPA dose was selected for use because the Sponsor postulated that this lower dose would be sufficient to oppose lower dose of CE in the prevention of endometrial hyperplasia. Furthermore, the Sponsor postulated that the 1.5 mg MPA dose may also "provide additional benefit to CE in the prevention of postmenopausal osteoporosis (b) (4) A placebo group was included for comparison in the analyses of VMS, VVA, and bone mineral density (BMD) assessments.

On September 25, 2001, the Sponsor submitted Type 6 NDA 21-396 to the Agency for the 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA combination dosage strengths for the prevention of postmenopausal osteoporosis. On July 25, 2002, the Sponsor received an Approvable action from the Agency for NDA 21-396 (Division of Metabolic and Endocrine Drug Products) with the request to address the following:

1. Taking into account the results of the Women's Health Initiative (WHI) study that were reported in the July 17, 2002 issue of JAMA, please provide an updated risk/benefit analysis of 0.45 mg1.5 mg and 0.3 mg/1.5 mg doses of Prempro™ when used in the prevention of postmenopausal osteoporosis.
2. Provide detailed analyses of the cardiovascular adverse event data from the HOPE trial. To the extent possible, the analyses should parallel those from the WHI study that were reported in the July 17, 2002 issue of JAMA. Consultation with DMEDP is strongly encouraged as you undertake the analysis.

3. In addition, during recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted. Before this application may be approved, all manufacturing facilities must obtain a satisfactory cGMP inspection.

On November 5, 2001, the Sponsor resubmitted the 0.3 mg CE/1.5 mg MPA dosage strength (withdrawn without prejudice from NDA 20-517/S-017) as NDA 20-527/S-024 for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause. The submission includes 2 years of data for the osteoporosis and metabolic subgroup (749 subjects). In addition, data from the 1-year interim analysis of the basic study group (total of 2,763 subjects including the 749 substudy subjects) is presented for VMS and VVA.

1.4. Other Relevant Information

The currently approved Prempro™ 2.5, Prempro™ 5, and Premphase® are marketed worldwide. A combination package of Premarin® with MPA is registered in 72 countries worldwide.

1.5. Important Issues with Pharmacologically Related Agents

Five estrogen/progestin combination drug products for oral administration are approved for market use in the US for HRT (Prempro™, Premphase®, Activelle™, femhrt®, and Ortho-Prefest®). One combination estrogen/progestin transdermal system is approved for market use in the US for HRT (Combipatch™).

2. SIGNIFICANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, AND/OR MICROBIOLOGY

2.1. Chemistry, Manufacturing and Controls

The conjugated estrogens found in Premarin® tablets are a mixture of (b) (4) estrogens derived from pregnant mares' urine including the sodium sulfate conjugates of estrone, equilin, 17α-dihydroequilin, 17β-dihydroequilin, 17α-estradiol, (b) (4) Medroxyprogesterone acetate is a synthetic progestin derived from 17α-hydroxyprogesterone.

The CE/MPA dosage form consists of a (b) (4)

Reviewer's Comments

Per the Chemistry, Manufacturing and Controls (CMC) Review, the application is approvable pending resolution of manufacturing deficiencies. Please see the Chemistry, Manufacturing and Controls Review for a full description of manufacturing deficiencies.

2.2. Animal Pharmacology and Toxicology

Please refer to the Pharmacology and Toxicology Review.

2.3. Microbiology

No Microbiology Review was conducted for this oral drug product.

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

3.1. Pharmacokinetics

Two clinical pharmacology studies (Studies 0713D2-119-US and 0713D2-120-US) were conducted to determine the pharmacokinetics and relative bioavailability of CE and MPA in a total of 61 healthy postmenopausal women. Six different dosage strengths were administered across these two pharmacokinetic studies. CE/MPA combinations included the 0.625 mg CE/2.5 mg MPA, 0.45 mg CE/2.5 mg MPA, 0.45 mg CE/1.5 mg MPA, and 0.3 mg CE/1.5 mg MPA tablets. CE-alone dosage strengths included the 0.3 mg and 0.45 mg tablets. Because of the lower dosage strengths, two tablets of each strength were given to provide plasma concentration that could be more accurately assayed.

In summary, the results of these two PK studies are as follows:
• two tablets of 0.45 mg CE/2.5 mg MPA(treatment B), 0.45 mg CE/1.5 mg MPA (treatment C), or 0.45 mg CE (treatment D) tablets produced lower estrogen concentrations than two tablets of 0.625 mg CE/2.5 mg MPA (treatment A); ratios of mean C_{max} for estrogens observed following treatments of B, C, and D to treatment A ranged from 56% to 76%, and the ratios of mean AUC ranged from 57% to 84%;
• MPA concentrations were lower with 0.45 mg CE/1.5 mg MPA tablets (treatment C) than with 0.625 mg CE/2.5 mg MPA (treatment A) or 0.45 mg CE/2.5 mg MPA tablets (treatment B); ratios of mean C_{max} following treatment C to treatments A and B were 53% and 68%, respectively; and the ratios of mean AUC were 62% and 63%, respectively; approximately 60% of the larger MPA dose.
• two tablets of 0.3 mg CE/1.5 mg MPA (treatment C) or 0.3 mg CE-alone (treatment D) produced lower estrogen concentrations than did two tablets of 0.625 mg CE/2.5 mg MPA (treatment A) or 0.45 mg CE/1.5 mg MPA tablets (treatment B); estrogen ratios of mean C_{max} for treatment B to those for treatment A ranged from 56% to 63%; estrogen ratios of mean C_{max} for treatments C and D to those of treatment A ranged from 46% to 54%, and the ratios of mean AUC ranged from 45% to 59%;
• MPA concentrations were lower with 0.3 mg CE/1.5 MPA (treatment C) or with 0.45 mg CE/1.5 mg MPA (treatment B) than with 0.625 mg CE/2.5 mg MPA tablets (treatment A); ratios of mean C_{max} for treatments B and C to the mean C_{max} for treatment A were 70% and 77%, respectively, and the ratios of mean AUC were 72% and 70%

These results show that CE and MPA behaved pharmacokinetically in a dose-related manner, and MPA had no effect on the pharmacokinetics of CE. However, because different formulations were used in Study 0713D2-120-US, linear dose-proportionality cannot be concluded.

The CE/MPA formulation for 0.3 mg CE/1.5 mg MPA used in the clinical study was identical to the to-be-marketed formulation in terms of scale of manufacture and composition, but differed in color coat. The clinical formulation was white. The to-be-marketed color coat is cream (0.3 mg CE/1.5 mg MPA). However, the Clinical and Biopharmaceutics Review indicates that the dissolution profiles between the clinical batch and the market batch appear to be similar for the 0.3 mg CE/1.5 mg MPA tablet despite the color change.

3.2. Pharmacodynamics

Please refer to the Clinical Pharmacology and Biopharmaceutics Review of NDA 20-527/S-017 (year 1 of the HOPE study).

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1. Source of Clinical Data

In NDA 20-527/S-024, the clinical development program consisted of two Phase 1 studies (Studies 0713D2-119-US and 0713D2-120-US and a large multicenter Phase 3 study (Study 0713D2-309-US) conducted in the US. The two Phase I studies were designed to describe the pharmacokinetics of the lower dose combination products (0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA). The Phase 3 study was designed to evaluate the impact of lower combination doses of CE/MPA on bone mineral density over a two-year period. This 2-year Phase 3 study was comprised of a basic study (year 1, total

of 2,673 treated women of which 749 are substudy subjects), and an osteoporosis and metabolic substudy (years 1 and 2, 749 women in the substudy group).

Completed study year 1 was analyzed and presented in NDA 20-527/S-017. Supplement-017 contained final data on 2,673 treated subjects (including the ≅ 749 substudy subjects) for endometrial safety, control of vasomotor symptoms, vaginal Maturation Index, and metabolic parameters (substudy subjects). An interim analysis of bone mineral density and bone-related metabolic parameters was not presented in the year 1 interim analysis. Year 2 of Study 0713D2-309-US was ongoing when NDA 20-527/S-017 was submitted on June 15, 2000. Please see the Medical Officer's review of NDA 20-527/S-017 for a full description of year 1 of the HOPE study.

One additional ongoing study in Japan is included in the submission. Study 0713D2-312-JA is a 1-year prevention of postmenopausal osteoporosis study comparing two doses of CE/MPA (0.625 mg CE/2.5 mg MPA/day and 0.3 mg CE/1.5 mg MPA/day) and 2 mg/day estriol.

4.2. Overview of Clinical Trials

See Table 1 for a summary of studies in the clinical development program.

Table 1: NDA 20-527/S-024 Clinical Development Program

Protocol No.	Study Design Status of Study	Treatment Group And Dose (mg)	Number of treated subjects
0713D2-119-US	Completed, single-dose, 4-period, 4-treatment, crossover design Phase 1 study of the comparative bioavailability of conjugated estrogens and medroxyprogesterone acetate	CE/MPA Group A: 2 x 0.625 mg/2.5 mg Group B: 2 x 0.45 mg/2.5 mg Group C: 2 x 0.45 mg/1.5 mg CE alone Group D: 2 x 0.45 mg	31
0713D2-120-US	Completed, single-dose, 4-period, 4-treatment crossover design Phase 1 study of the comparative bioavailability of conjugated estrogens and medroxyprogesterone acetate	CE/MPA Group A: 2 x 0.625 mg/2.5 mg Group B: 2 x 0.45 mg/1.5 mg Group C: 2 x 0.3 mg/1.5 mg CE alone Group D: 2 x 0.3 mg	30
0713D2-309-US	Interim 1-year prospective, double-blind, randomized, Phase 3 study of multiple doses of conjugated estrogens and conjugated estrogens plus medroxyprogesterone acetate in postmenopausal women	Group A: 0.625 mg CE Group B: 0.625 mg CE/2.5 mg MPA Group C: 0.45 mg CE Group D: 0.45 mg CE/2.5 mg MPA Group E: 0.45 mg CE/1.5 mg MPA Group F: 0.3 mg CE Group G: 0.3 mgCE/1.5 mg MPA Group H: Placebo	348 331 338 340 331 326 327 332
0713D2-309-US	Completed, 2-year prospective, double-blind, randomized, Phase 3 substudy of multiple doses of conjugated estrogens and conjugated estrogen plus medroxyprogesterone acetate in postmenopausal women	Group A: 0.625 mg CE Group B: 0.625 mg CE/2.5 mg MPA Group C: 0.45 mg CE Group D: 0.45 mg CE/2.5 mg MPA Group E: 0.45 mg CE/1.5 mg MPA Group F: 0.3 mg CE Group G: 0.3 mgCE/1.5 mg MPA Group H: Placebo	97 86 95 96 94 89 98 94
0713D2-312-JA	Ongoing, 52-week, randomized, double-blind, double-dummy comparison of conjugated estrogens plus medroxyprogesterone acetate and estriol in postmenopausal women	0.625 mg CE/2.5 mg MPA 0.3 mg CE/1.5 mg MPA 2.0 mg estriol	≅ 360 subjects, approx. 120 per group

Source: Adapted from NDA 20-527/S-024.

The protocol for Study 0713D2-309-US, originally submitted on January 13, 1994 and finalized on July 18, 1995, was amended on February 23, 1999. This amendment specified that an interim analyses of data by treatment group, but not individual subject data, would be provided confidentially to individuals at the National Institutes of Health (NIH) for subjects assigned to treatment after August 23, 1995 through July 31, 1998. Prestudy and cycle 6 data, reported as either mean percent change from baseline or mean change from baseline, was provided for the following parameters:
high density lipoprotein cholesterol (HDL-C)
high-density lipoprotein$_2$ cholesterol (HDL$_2$-C)
low-density lipoprotein cholesterol (LDL-C)
lipoprotein (LP) (a)
fibrinogen activity
factor VIII activity
antithrombin III activity
plasminogen activator inhibitor-1 (PAI-1) antigen

In order to ensure that the blind to individual subject treatment assignments was maintained, only data summaries were prepared (by a third party statistician), so as not to effect the conduct of the study. The Division of Reproductive and Urologic Drug Products (DRUDP) provided statistical comments and recommendations regarding the interim analyses of lipid and coagulation data from the study (letter dated April 22, 1999). The submission provides no information on the intended use of the lipid and coagulation data submitted to the NIH.

In a December 9, 1999 submission to IND 21,696, an unblinding strategy was devised in order to assemble and analyze interim data for NDA 20-527/S-017 and to preserve the integrity of the ongoing HOPE substudy (see NDA 20-527/S-017, Addendum 2, Unblinding Procedures for Interim Analysis of HOPE Study, Volume 52, page 288). The Division concurred with the proposed unblinding procedures on December 16, 1999.

4.3. Postmarketing Experience

Prempro™ 2.5, Prempro™ 5, and Premphase® have been marketed for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause, the prevention of postmenopausal osteoporosis since approval in 1994. The Sponsor has submitted regular Quarterly Adverse Experience Reports and Annual Reports to the NDA file.

4.4. Literature Review

Numerous references are available that pertains, generally and specifically, to the overall risks and benefits of both estrogen-alone therapy and estrogen/progestin therapy. No additional FDA literature review was conducted.

5. CLINICAL REVIEW METHODS

5.1. Describe How Review was Conducted

Data from two Pharmacokinetic Phase 1 Studies (Studies 0713D2-119-US and 0713D2-120-US), and year 1 (interim analysis) of a single 2-year, Phase 3 clinical trial (Study 0713D2-309-US, the HOPE study) were reviewed in detail under NDA 20-527/S-017 (submission dated June 15, 2000). On October 16, 2000, the 4-Month Safety Update for the HOPE study was reviewed in detail. The 4-Month Safety Update summarized all relevant safety data for the HOPE study from December 23, 1999 (the cutoff date for the 1-year interim analysis) to August 2, 2000. On July 18, 2001, the Second Safety Update for the HOPE study, covering the period August 3, 2000 through April 2, 2001 was reviewed in detail.

NDA 20-527/S-024, substudy year 1 and 2 of Study 0713D2-309-US, was submitted electronically on November 7, 2001. Supplement-024, containing data from the completed HOPE study for the osteoporosis and metabolic substudy group, was reviewed in its entirety.

The 4-Month Safety Update for NDA 20-527/S-024, submitted on March 5, 2002, was reviewed in detail. This 4-Month Safety Update summarizes all relevant safety data for Study 0713D2-309-US from April 1, 2001 through January 31, 2002, and for Study 0713D2-312-JA (now completed but still blinded) from December 31, 2000 through January 31, 2002.

5.2. Overview of Materials Consulted in Review

NDA 20-527/S-024 was submitted electronically on November 7, 2001. The 4-Month Safety Update was submitted electronically on March 4, 2001. On March 29, 2001, the Sponsor submitted an electronic correction to the 4-Month Safety Update. The dosage group for Subject 30914-0055 was corrected from 0.45 mg CE alone to 0.45 mg CE/1.5 mg MPA.

5.3. Overview of Methods Used to Evaluate Data Quality and Integrity

No DSI audit was requested. Conjugated estrogens and medroxyprogesterone acetate are approved drugs and longstanding efficacy and safety data are available for both drugs. Based on extensive clinical experience with the approved higher dosage strengths of Prempro™ for the treatment of VMS and VVA, it was determined that this supplemental NDA had no specific safety concerns and did not require inspection.

5.4. Were Trials Conducted in Accordance with Accepted Ethical Standards

The informed consent document proposed for use in Study 0713D2-309-US was appropriate. Appropriate standards of patient care were administered during the conduct of the clinical trial in accordance with regulations pertaining to Good Clinical Practice (GCP). One study site (#30952) was terminated due to non-compliance with Good Clinical Practice.

5.5. Evaluation of Financial Disclosure

Thirty-nine (39) clinical investigators did not respond to the request for financial disclosure. Twenty-one (21) of the 39 non-responders were no longer at the study site and three were deceased. Three clinical investigators reported receiving approximately $25,000 - $28,000 for participation in the (b) (6) . These three clinical investigators enrolled between (b) (4) subjects. One clinical investigator, (b) (6) , is a member (b) (6) subjects. Due to the small number of enrolled subjects at these three sites, no concerns arise from this financial disclosure information.

6. INTEGRATED REVIEW OF EFFICACY

6.1. Brief Statement of Conclusions

The data presented in NDA 20-527/S-024 provides sufficient evidence from one placebo-controlled clinical trial to support the safety and efficacy of the 0.3 mg CE/1.5 mg MPA dosage strength, taken daily, for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause, and protection of the endometrium from equivalent estrogen-induced endometrial hyperplasia.

6.2. General Approach to Review of the Efficacy of the Drug

Study 0713D2-309-US, originally submitted in NDA 20-527/S-017, was comprised of two parts: 1) a 1-year basic study with a total of 2,673 postmenopausal women (including 749 subjects assigned to the

osteoporosis and metabolic substudy group), and 2) a 2-year osteoporosis and metabolic substudy with 749 postmenopausal women. In NDA 20-527/S-017, an interim analysis of the 1-year basic study was presented. NDA 20-527/S-017 received an Approvable action for the 0.45 mg CE/1.5 mg MPA dosage strength for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause in women with a uterus, and protection of the endometrium.

In this submission, year 1 interim data for the 8 treatment groups in Study 0713D2-309-US is resubmitted. In addition, year 1 and year 2 data for the 8 treatment groups in Study 0713D2-309-US is presented for the 749 subjects in the osteoporosis and metabolic substudy. A summary of an ongoing osteoporosis study in Japan (Study 713D2-312-JA) is also included in the submission.

6.3. Detailed Review of Trials by Indication

Study 0713D2-309-US utilized a double-dummy design and 8 possible drug regimens. The CE and CE/MPA tablets and the corresponding placebo tablets were provided by Wyeth-Ayerst Research in 7-day blister cards. Four 7-day blister cards were dispensed for each 28-day cycle. Subjects were encouraged to take the study medication at approximately the same time each day. Subjects were assigned to Groups A, B, C, D, E, F, G, or H according to a computer-generated randomization table. Block randomization was used to ensure a balanced allocation of subjects into the groups summarized below:

Group (N)	CE (mg)	CE/MPA (mg)
A (348)	0.625	Placebo
B (331)	Placebo	0.625/2.5
C (338)	0.45	Placebo
D (340)	Placebo	0.45/2.5
E (331)	Placebo	0.45/1.5
F (326)	0.3	Placebo
G (327)	Placebo	0.3/1.5
H (332)	Placebo	Placebo

In addition to the above study medication, all study subjects received Caltrate®, elemental calcium, 600 mg, to be taken once daily. Therefore, each subject took three tablets daily, two tablets of study mediation and 1 Caltrate® tablet.

Effects on Bone Mineral Density

The primary efficacy variable for the 2-year substudy population in the HOPE study was the prevention of postmenopausal bone loss. Prevention of bone loss was assessed using measurements of bone mineral density (BMD) by dual energy x-ray absorptiometry (DXA). The primary parameter was the BMD of the anteroposterior lumbar spine (L2 to L4). BMD measurements of the total body, femoral neck, and trochanter were also analyzed. Serum osteocalcin, urinary calcium, and urinary N-telopeptide were used as bone turnover markers (BTM) at cycles 6, 13, 19, and 26. Please see the Division of Metabolic and Endocrine Drug Products (DMEDP) Medical Officer's Review of the Type 6 NDA 21-396 for a full description of the osteoporosis and metabolic data for the 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA dosage strengths.

Effects on Vasomotor Symptoms

Please refer to the Medical Officer's Review of NDA 20-527/S-017, dated April 6, 2001, for a full description of the vasomotor symptoms data in year 1 of the HOPE study. The analysis of vasomotor symptoms at the 1-year time point was considered a final analysis for the basic study population. However, subjects in the osteoporosis and metabolic substudy continued to complete daily diary cards with hot flush data. In this submission, measurements of the relief of vasomotor symptoms in year 2 are considered secondary efficacy endpoints.

For the 2,673 treated subjects in year 1 of the HOPE study (basic study group), only 9% of treated subjects (241 of 2,673 subjects) met the inclusion criterion of 7 to 8 moderate-to-severe vasomotor symptoms per day or 50 per week at baseline (VMS subset). These 241 subjects were, however, equally divided between the 8 treatment groups (range between 27 to 34 subjects per group).

The reported number and severity of hot flushes were assessed by evaluation of the subject's daily diary. The average daily severity score was calculated as the sum of the daily severity scores/number of days for which data were available. The daily severity score was calculated as follows:

[(the number of mild hot flushes) x1 + (the number of moderate hot flushes) x 2 + (the number of severe hot flushes) x 3]/the total number of hot flushes on that day.

In the Medical Officer's review of year 1 of the HOPE study, the Sponsor's submitted "EE population" analysis (more commonly referred to as the ITT population by the reviewer) by week was analyzed because it included:

- all subjects randomly assigned to the study who had at least 7 moderate-to-severe baseline hot flushes recorded on each of the last 7 days of the screening diary card, or at least 50 moderate-to-severe hot flushes on the last 7 days combined;
- subjects who recorded taking study medication at least once, and
- subjects who completed at least one on-treatment visit.

During the review of NDA 20-527/S-017, the Sponsor provided upon request, the frequency and severity data for the ITT subset population, as defined above, with last observation carried forward (LOCF) approach showing the baseline, weeks 4, 8, and 12 mean number and severity of hot flushes and the mean change from baseline for each of the 8 treatment groups as compared to placebo.

As shown in Table 2, the 0.3 mg CE/1.5 mg MPA dosage strength is effective in reducing the number of moderate-to-severe hot flushes at weeks 4, 8, and 12 as compared to placebo ($p<0.001$ at all time points).

Table 2: Change in the Mean Number of Moderate-to-Severe Hot Flushes During Therapy in Subjects with ≥ 7 Moderate-to-Severe Hot Flushes at Baseline, ITT Population, LOCF

Week	Group E 0.3 mg CE/1.5 mg MPA[a] N = 33 of 327 (10%)	Group H Placebo N = 28 of 332 (8%)
Baseline		
Mean Number	11.30	11.69
Week 4		
Mean Number	4.01	8.09
Mean Change[b]	-7.60	-3.80
p-value vs. placebo[c]	<0.001	-
Week 8		
Mean Number	2.63	6.93
Mean Change[b]	-8.84	-4.86
p-value vs. placebo[c]	<0.001	-
Week 12		
Mean Number	1.47	5.81
Mean Change[b]	-10.00	-5.98
p-value vs. placebo[c]	<0.001	-

Source: Adapted from data provided by the Sponsor on March 15, 2001.

[a] mg of conjugated estrogens/mg of medroxyprogesterone acetate.

[b] Mean change from baseline.

[c] Based on analysis of covariance with treatment as factor and baseline as covariate.

Table 3 shows the analyses of the change from baseline in the mean severity of hot flushes for weeks 4, 8, and 12. The 0.3 mg CE/1.5 mg MPA dosage strength is effective in reducing the severity of hot flushes at all time points ($p<0.001$ at all time points).

Table 3: Change from Baseline in the Severity of Hot Flushes During Therapy in Subjects with ≥ 7 Moderate-to-Severe Hot Flushes at Baseline, ITT Population, LOCF

Week	Group E 0.3 mg CE/1.5 mg MPA[a] N = 33 of 327 (10%)	Group H Placebo N = 28 of 332 (8%)
Baseline		
Mean Severity	2.24	2.37
Week 4		
Mean Severity	1.48	2.03
Mean Change[b]	-0.79	-0.29
p-value vs. placebo[c]	<0.001	
Week 8		
Mean Severity	0.93	1.76
Mean Change[b]	-1.34	-0.57
p-value vs. placebo[c]	<0.001	
Week 12		
Mean Severity	0.58	1.62
Mean Change[b]	-1.67	-0.72
p-value vs. placebo[c]	<0.001	

Source: Adapted from data provided by the Sponsor on March 15, 2001.
[a] mg of conjugated estrogens/mg of medroxyprogesterone acetate.
[b] Mean change from baseline.
[c] Based on analysis of covariance with treatment as factor and baseline as covariate.

One interesting observation across the 8 treatment groups in study year 1, however, results from a subgroup analysis of VMS by age in subjects who completed 12 treatment weeks. Although the demographics and baseline characteristics for the VMS subset were not evaluated in the submission, supportive tables in the submission showed that the majority of the VMS subset subjects were in the 50 to 59 age group with less in the < 50 age group and fewer in the ≥ 60 age group. While the age subgroup numbers are too small to permit conclusions, they show interesting differences in treatment effect. Results by age group (< 50, 50 to 59, ≥ 60) demonstrate selected reduced or delayed treatment effect (reduction in frequency and severity of hot flushes) in women < 50 years of age compared to women 50 to 59 years of age. In the 50 to 59 age subgroup, a statistically significant reduction in the frequency and severity of hot flushes ($p<0.001$) was demonstrated at all time points (weeks 4, 8, and 12). In women < 50 years of age, a statistically significant treatment effect was also demonstrated by the 0.45 mg CE/1.5 mg MPA dosage strength at all time points. This was not the case, however, for the 0.3 mg CE/1.5 mg MPA dosage strength, which showed a delay in treatment effect until week 8 for frequency ($p=0.86$ at week 4, $p=0.024$ at week 8), and no treatment effect for severity at any time point ($p=0.065$ at week 4, $p=0.25$ at week 8, and $p=0.28$ at week 12). The ≥ 60 age group had too few women to permit an observational assessment of treatment effect. However, no conclusion can be drawn from these observational findings.

In this submission, the Sponsor submitted summary tabulations of the frequency and severity of hot flushes, adjusted means and comparisons between the seven active-treatment groups and the placebo group in the modified ITT population for the osteoporosis and metabolic subgroup for cycles 3, 6, 13, 19, and 26. The modified ITT population included all subjects who were randomly assigned to treatment, who received study medication, and who had at least 1 baseline hot flush recorded in the last 7 days of screening diary card before the start of study medication. Only this population was analyzed for the secondary efficacy variable of hot flushes. No analysis was submitted in NDA 20-527/S-024 for those substudy subjects who met the inclusion criteria of 7 to 8 MSVS (or at least 50 per week) at baseline. Per the submission, however, all active-treatment groups had fewer hot flushes and a greater decrease in the severity of hot flushes compared to placebo for cycles 3, 6, 13, 19, and 26.

Reviewer's Comments

The analysis of the frequency and severity of vasomotor symptoms at the 1-year time point was considered a final analysis for the basic study population for a VMS indication.

The modified ITT population by cycle, as defined in NDA 20-527/S-024, does not meet the 1995 HRT Guidance for either the entry criteria or the recommended analysis for a VMS indication. The 1995 HRT Guidance states, "Entry criteria for the indication of moderate-to-severe vasomotor symptoms should require enrolled subjects to have a minimum of 7 to 8 moderate-to-severe hot flushes per day, or 50 to 60 per week at baseline." Therefore, the submitted modified ITT population analysis by cycle, submitted in NDA 20-527/S-024, will not be considered in this review.

From the data presented in the 1-year interim analysis of Study 0713D2-309-US, the 0.3 mg CE/1.5 mg MPA dosage strength is effective in reducing the number and severity of moderate – to-severe hot flushes at weeks 4, 8, and 12 as compared to placebo ($p<0.001$ at all time points). The 0.3 mg CE/1.5 mg MPA dosage strength should be approved for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause.

Effects on Vulvar and Vaginal Atrophy

A vaginal cytological smear was obtained at the prestudy visit and during cycles 6 and 13 for the year-1 basic study group to determine the Maturation Index (MI). A MI is reported as the proportion of vaginal superficial cells, relative to the number of parabasal and intermediate cells, in a lateral vaginal wall smear. MI data was analyzed within treatment groups by the change from baseline using the Wilcoxon matched pairs signed-rank test and among groups using Wilcoxon's rank-sum test. However, data in the Supplement-017 submission represented median rather than mean change from baseline. Upon request, the Sponsor provided data demonstrating the mean change from baseline at cycle 6 and cycle 13 on March 22, 2001. See Table 4. Please refer to the Medical Officer's Review of NDA 20-527/S-017, dated April 6, 2001, for a full description of the vaginal Maturation Index data in year 1 of the HOPE study.

The Maturation Index results show that the percentages of vaginal superficial cells increased significantly from screening values at cycles 6 and 13, and the differences were statistically significant from placebo for the 0.3 mg CE/1.5 mg MPA dosage strength ($p<0.001$). A corresponding statistically significant decrease in the percentage of vaginal parabasal cells was likewise demonstrated at cycles 6 and 13 ($p<0.001$ at both time points).

Table 4: Subjects with Maturation Index Results, Mean Value and Comparison Between Prempro™ 0.3 /1.5 and Placebo by Cycle, Intent-to-Treat Population with LOCF

Treatment[a] (N) Type of Cell	Percentage of Epithelial Cells (%)			
	Baseline Mean ± SE	Cycle 6 Mean Change ± SE	Cycle 13 Mean Change ± SE	p-Value vs. Placebo[b] Cycle 6 – Cycle 13
Group E (n = 316) 0.3 mg CE/1.5 mg MPA				
Superficial Cells	7.1 ± 0.7	9.4 ± 1.1	9.7 ± 1.0	<0.001 - <0.001
Intermediate Cells	59.6 ± 2.0	17.2 ± 2.0	18.2 ± 2.1	<0.001 - <0.001
Parabasal Cells	33.3 ± 2.3	-26.6 ± 2.2	-27.9 ± 2.3	<0.001 - <0.001
Group H (n = 321) Placebo				
Superficial Cells	6.8 ± 0.6	0.8 ± 1.0	0.7 ± 1.0	<0.001 - <0.001
Intermediate Cells	56.8 ± 2.1	-3.2 ± 2.0	-3.1 ± 2.1	<0.001 - <0.001
Parabasal Cells	36.5 ± 2.3	2.4 ± 2.2	2.3 ± 2.2	<0.001 - <0.001

Source: Adapted from data provided by the Sponsor on March 22, 2001.
[a] Identified by dose (mg) of CE or CE/MPA. [b] Based on analysis of variance.

In the year-2 substudy (NDA 20-527/S-024), data in the submission also represents median rather than mean change in the MI from baseline at cycles 6, 13, 19 and 26. Since the analysis of the Maturation Index at the 1-year time point was considered a final analysis and the measurement of the changes in the vaginal maturation index during year 2 of Study 0713D2-309-US was considered a secondary efficacy endpoint, the data in NDA 20-527/S-024 will not be considered in this review.

Reviewer's Comments

From the data presented in the 1-year interim analysis of Study 0713D2-309-US, the percentages of vaginal superficial cells increased significantly from baseline at cycles 6 and 13, and the differences are statistically different from placebo for the 0.3 mg CE/1.5 mg MPA dosage strength. A corresponding decrease in the percentage of vaginal parabasal cells was demonstrated at cycles 6 and 13, and the differences are statistically different from placebo for the 0.3 mg CE/1.5 mg MPA dosage strength. The 0.3 mg CE/1.5 mg MPA dosage strength should be approved for the treatment of vulvar and vaginal atrophy associated with the menopause.

Effects on the Endometrium

For study year 1of the HOPE study, the primary efficacy measure was an assessment of the incidence of endometrial hyperplasia (or endometrial cancer) made by endometrial biopsy. In year 1 of Study 0713D2-309-US, endometrial biopsies were obtained at cycles 6 and 13. The population of interest was an efficacy-evaluable population. Evaluable subjects are those who had a prestudy endometrial biopsy, had taken at least one dose of study medication, and had an endometrial biopsy performed during cycles 5 to 7 and cycles 12 to 14 or who developed endometrial hyperplasia (or endometrial cancer) at any time during the first year of the study. The analysis done at that time was considered a final analysis for the 2,153 evaluable subjects in the basic study. Please refer to the Medical Officer's Review of NDA 20-527/S-017, dated April 6, 2001, for a full description of the endometrial biopsy data in year 1 of the HOPE study.

For study year 2 of the HOPE study, the incidence of endometrial hyperplasia (or cancer) was a secondary efficacy measure. Endometrial biopsies were performed at cycle 19 and at cycle 26 (end-of-study) for the substudy subjects.

In Study 0713D2-309-US (both the basic 1-year study and the 2-year osteoporosis and metabolic substudy), the study procedure for determination of final endometrial biopsy diagnosis complied with the proposed revised 1995 HRT Guidance, namely: 1) agreement of the two independent, blinded primary pathologists; 2) if disagreement, a third independent, blinded pathologist was consulted; 3) final diagnosis based on the diagnosis of the majority decision (two out of three pathologists agree) or "worse-case scenario" if all three pathologists disagree. A total of 2,153 subjects were included in the primary efficacy analysis of endometrial hyperplasia or cancer at cycle 13. Five hundred twenty (520) subjects were excluded because no valid endometrial biopsy was obtained between cycles 12 to 14 and no endometrial hyperplasia was diagnosed before cycle 12. One of these subjects did not have a prestudy endometrial biopsy performed.

No endometrial carcinoma was reported during the first year of the HOPE study. However, two subjects had endometrial biopsy readings of endometrial carcinoma in the interim analyses submitted. The endometrial biopsy pathology reports for Subject 30912-0049 (age 58) in Group E (0.45 mg CE/1.5 mg MPA) and Subject 30924-0011 (age 63) in Group F (0.3 mg CE) were reviewed by the clinical review team (the reviewer, a second medical officer [also a board-certified pathologist], and the team leader). For Subject 30912-0049, the clinical review team agreed that the final diagnosis for this subject should be well-differentiated endometrial adenocarcinoma, based on the information submitted. In this case, the majority decision (two of the three pathologists) was well-differentiated adenocarcinoma in a polyp, based on the "original" endometrial biopsy slides readings. For Subject 30924-0011, the clinical review team followed the most conservative approach and accepted the "worst-case" diagnosis of endometrial adenocarcinoma rendered by pathologist 2 because accepting

the majority decision (two of the three pathologists) would incorporate the diagnosis of an unblinded gynecologic oncologist outside the study. In this case, the third blinded, adjudicating pathologist was not consulted (which is in violation of the protocol-specified procedure).

As a result of the reclassification of two cases of reported hyperplasia as endometrial adenocarcinoma, a total of 30 subjects developed endometrial hyperplasia by cycle 13 (1.4%, 30 of 2,153 evaluable endometrial biopsies across all 8 treatment groups), and 2 subjects developed endometrial adenocarcinoma in the first year of the HOPE study.

Twenty-nine (29) of the cases of endometrial hyperplasia occurred in the CE alone treatment groups. Only 1 case of endometrial hyperplasia occurred in a CE/MPA group (0.3 mg CE/1.5 mg MPA). Table 5 shows the incidence of endometrial hyperplasia alone (not endometrial hyperplasia or cancer) for the efficacy evaluable population in year 1 of Study 0713D2-309-US.

Table 5: Incidence of Endometrial Hyperplasia at Cycle 13, Year 1 of Study 0713D2-309-US, EE Population

Treatment by dose (mg) of CE or CE/MPA	N	Total Number Hyperplasia[a]	Hyperplasia Rate (%)	One-sided 95% C1 (%)[b]	p-Value vs. CE alone[c]
Group A 0.625 mg CE	249	20	8.03	(0, 11.5)	--
Group B 0.625 mg CE/2.5 mg MPA	278	0	0.00	(0, 1.1)	<0.001
Group C 0.45 mg CE	279	9	3.23	(0, 5.6)	--
Group D 0.45 mg CE/2.5 mg MPA	273	0	0.00	(0, 1.1)	0.004
Group E 0.45 mg CE/1.5 mg MPA	272	0	0.00	(0, 1.2)	0.004
Group F 0.3 mg CE	269	0	0.00	(0, 1.1)	--
Group G 0.3 mg CE/1.5 mg MPA	272	1	0.37	(0, 1.8)	1.00
Group H Placebo	261	0	0.00	(0, 1.2)	--

Source: Adapted from Table 9.2.2.1A, NDA 20-527/S-017, Volume 53, page 96.
[a] Total number of hyperplasias calculated as number of patients.
[b] Confidence intervals calculated by the statistical reviewer.
[c] Individual pairwise comparisons: Groups B with A; D and E with C; G with F, based on Fisher' exact test. Two-sided p-values are shown.

However, endometrial hyperplasia or endometrial cancer were reported in treatment groups in Study 0713D2-309-US. Table 6 shows the incidence rates for hyperplasia or cancer when the cases of endometrial hyperplasia or cancer are combined.

Table 6: Incidence of Endometrial Hyperplasia or Cancer at Cycle 13, Year 1 of Study 0713D2-309-US, EE Population

Treatment by dose (mg) of CE or CE/MPA	N	Total Number Hyperplasia/ Carcinoma[a]	Hyperplasia Rate (%)	One-sided 95% C1 (%)[b]	p-Value vs. CE alone[c]
Group A 0.625 mg CE	249	20	8.03	(0, 11.5)	--
Group B 0.625 mg CE/2.5 mg MPA	278	0	0.00	(0, 1.1)	<0.001
Group C 0.45 mg CE	279	9	3.23	(0, 5.6)	--
Group D 0.45 mg CE/2.5 mg MPA	273	0	0.00	(0, 1.1)	0.004

Group E 0.45 mg CE/1.5 mg MPA	272	1[d]	0.37	(0, 1.8)	0.020
Group F 0.3 mg CE	269	1[e]	0.37	(0, 1.8)	--
Group G 0.3 mg CE/1.5 mg MPA	272	1	0.37	(0, 1.8)	1.00
Group H Placebo	261	0	0.00	(0, 1.2)	--

Source: Prepared by the Division from combined numbers of hyperplasia or cancer.
[a] Total number of hyperplasias or cancer calculated as number of patients.
[b] Confidence intervals calculated by the statistical reviewer.
[c] Individual pairwise comparisons: Groups B with A; D and E with C; G with F, based on Fisher' exact test. Two-sided p-values are shown.
[d] Hyperplasia reclassified as cancer by the clinical review team for NDA 20-527/S-017.
[e] Hyperplasia reclassified as cancer by the clinical review team for NDA 20-527/S-017.

Reviewer's Comments

The occurrence of one case of endometrial adenocarcinoma in the 0.3 mg CE alone treatment group and one case of endometrial adenocarcinoma in the 0.45 mg CE/1.5 mg MPA treatment group in year 1 of Study 0713D2-309-US is no higher than that seen in other large, prospective controlled trials. Although the occurrence of endometrial adenocarcinoma is a rare event in a controlled clinical trial, zero to one case of endometrial adenocarcinoma has been reported in either estrogen alone or estrogen/progestin treatment groups for other large, controlled HRT clinical trials.

The reported 1-year incidence rates of endometrial hyperplasia are approximately 0-1% for non-treated women and women treated with currently marketed combination HRT regimens, including Prempro™ 2.5, Prempro™ 5, and Premphase®. Per the proposed revision of the 1995 HRT Guidance, for combination drug products intended to demonstrate endometrial safety, the results of a clinical trial should demonstrate a hyperplasia rate that is less than or equal to 1% with an upper bound of a one-sided 95% confidence interval for that rate which does not exceed 4% at one year.

Results from year 1 of Study 0713D2-309-US shows an incidence of 0.37% for the combined endometrial hyperplasia or cancer rate for the 0.3 mg CE/1.5 mg MPA dosage strength, and the upper bound of a one-sided 95% confidence interval of 0, 1.8, well below the one-sided 95% confidence interval upper bound of 4%.

In the NDA 20-527/S-017 submission, rates of endometrial hyperplasia at 1 year were analyzed by age groups (<50, 50 to 59, and ≥ 60 years of age). Utilizing a combined hyperplasia or cancer rate, subjects who were < 50 years of age had the lowest rate of endometrial hyperplasia or cancer regardless of their treatment group (0.45 %, 2 cases of endometrial hyperplasia or cancer in 446 subjects < 50). The hyperplasia or cancer rate in subjects 50 to 59 years of age, across all treatment groups, was 1.37% (20 cases of endometrial hyperplasia or cancer in 1,454 subjects between ages 59 to 60). Subjects who were ≥ 60 years of age had the highest endometrial hyperplasia or cancer rate (3.56%, 9 cases of endometrial hyperplasia or cancer in 253 subjects in the ≥ 60 years age group).

No subgroup analysis of hyperplasia rates by age groups was provided in this submission.

Reviewer's Comments

These findings strengthen the need for prompt endometrial evaluations, when needed to investigate vaginal bleeding in women on HRT therapy, especially for women 60 years of age and older.

An analysis of endometrial hyperplasia or cancer by ethnic origin was also provided in the Supplement-017 (interim year 1 data). However, the majority of study subjects were white (89%, 1,927 out of 2,153 evaluable subjects), and all but 2 subjects with endometrial hyperplasia or cancer identified their race as white.

No subgroup analysis of endometrial hyperplasia by ethnic origin was provided in this submission.

Reviewer's Comments

Overall, the incidence of abnormal endometrial pathology in year 1 of Study 0713D2-309-US is low. Thirty subjects (30), across the 8 treatment groups, developed endometrial hyperplasia (1.4%, 30 cases in 2,153 evaluable subjects), and 2 subjects developed endometrial carcinoma. Other large controlled studies of estrogen alone or estrogen/progestin-combination HRT drug products have reported endometrial hyperplasia rates ranging from 0% to 40%, and zero to one case of endometrial cancer. The results in Study 0713D2-309-US are consistent with these findings.

The data presented in Table 6 shows a dose-dependent response in endometrial hyperplasia or cancer within the CE alone groups with the 0.625 mg CE alone treatment group producing the highest endometrial hyperplasia rate and the 0.30 mg CE alone treatment group producing the lowest endometrial hyperplasia rate:

- **hyperplasia rate of 8.03% in Group A (0.625 mg CE)**
- **hyperplasia rate of 3.23% in Group C (0.45 mg CE)**
- **hyperplasia/rate of 0.37% in Group F (0.3 mg CE).**

No case of hyperplasia was reported in the placebo group.

Proportionally fewer postmenopausal women with an intact uterus developed endometrial hyperplasia or cancer taking the lower CE alone dosage strengths than with 0.625 mg CE alone.

The data in Table 6 also demonstrates that the combined endometrial hyperplasia or cancer rate is lower in the CE/MPA treatment groups than in the corresponding CE alone groups with the exception of the 0.3 mg CE alone (Group F) and the 0.3 mg CE/1.5 mg MPA (Group G) groups as shown below:

CE alone groups		CE/MPA groups
• 8.03% in Group A (0.625)	versus	0.00% in Group B (0.625/2.5)
• 3.23% in Group C (0.45)	versus	0.00% in Group D (0.45/2.5
• 3.23% in Group C (0.45)	versus	0.37% in Group E (0.45/1.5)
• 0.37% in Group F (0.3)	versus	0.37% in Group G (0.3/1.5)

Nonetheless, in year 1 of the HOPE study, the endometrial hyperplasia or cancer rate for all of the CE/MPA combination dosage strengths is below 1% and the upper bound of the one-sided 95% confidence interval for that rate is 1.8 or lower. See Table 6.

In this submission (NDA 20-527/S-024), the osteoporosis and metabolic substudy group had endometrial biopsies performed at cycle 19 and cycle 26 (end-of-study). The same procedure for reading the endometrial biopsy slides and the same pathologists participated through to the end of year 2.

Of the 749 subjects randomized in the 2-year osteoporosis and metabolic substudy in Study 0713D2-309-US, 608 substudy subjects had evaluable endometrial biopsies at cycle 13, and 518 substudy subjects had evaluable biopsies at cycle 26. The data for the 608 evaluable substudy subjects at cycle

13 is included in the Medical Officer's Review of NDA 20-527/S-017 and in the above discussion of endometrial hyperplasia and cancer.

In this submission, no cases of endometrial hyperplasia were reported in any of the combination CE/MPA treatment groups in the osteoporosis and metabolic substudy (0.625 mg CE/2.5 mg MPA, 0.45 mg CE/2.5 mg MPA, 0.45 mg CE/1.5 mg MPA, and 0.3 mg CE/1.5 mg MPA). Likewise, no cases of endometrial hyperplasia were reported in the placebo group in the osteoporosis and metabolic substudy. Within the CE-alone treatment groups (0.625 mg CE, 0.45 mg CE, and 0.3 mg CE), however, a dose-response was demonstrated.

For subjects in the osteoporosis and metabolic substudy at cycle 13, 7 cases of endometrial hyperplasia were reported in the 0.625 mg CE alone treatment group (10.4%, 7 of 67 subjects), 5 cases of endometrial hyperplasia were reported in the 0.45 mg CE alone treatment group (6.6%, 5 of 76 subjects), and 0.0% was reported in the 0.3 mg CE treatment group (0 of 74 subjects). Therefore, 12 of the 30 cases of endometrial hyperplasia diagnosed at cycle 13 in year 1 of the HOPE study occurred in substudy subjects. A total of 15 additional cases of endometrial hyperplasia in substudy subjects were documented after cycle 13 and either before or at cycle 26 (i.e., diagnosed within the second year of the HOPE study). In year 2, eight of the 15 cases of endometrial hyperplasia occurred in substudy subjects receiving 0.625 mg CE alone 14.5%, 8 of 55 subjects), 5 cases of endometrial hyperplasia occurred in the 0.45 mg CE alone group (7.46%, 5 of 67 subjects), and 2 cases of endometrial hyperplasia occurred in the 0.3 mg CE alone treatment group (2.66%, 2 of 63 subjects). See Table 7 for a comparison of years 1 and 2 in the osteoporosis and metabolic substudy group.

Table 7: Osteoporosis and Metabolic Substudy Group, Incidence of Endometrial Hyperplasia at Cycle 13 (Year 1) and at Cycle 26 (Years 2), Study 0713D2-309-US

	Year 1 Substudy Group			Year 2 Substudy Group		
Treatment by dose (mg) of CE or CE/MPA	N	Total Number Hyperplasia[a]	Hyperplasia Rate (%)	N	Total Number Hyperplasia[a]	Hyperplasia Rate (%)
Group A 0.625 mg CE	67	7	10.4	55	8	14.5
Group B 0.625 mg CE/2.5 mg MPA	76	0	0.00	62	0	0.00
Group C 0.45 mg CE	76	5	6.58	67	5	7.46
Group D 0.45 mg CE/2.5 mg MPA	78	0	0.00	66	0	0.00
Group E 0.45 mg CE/1.5 mg MPA	75	0	0.00	69	0	0.00
Group F 0.3 mg CE	74	0	0.00	63	0	0.00
Group G 0.3 mg CE/1.5 mg MPA	83	0	0.00	75	2	2.66
Group H Placebo	79	0	0.00	61	0	0.00

Source: Adapted from Final Report CSR-41303, Tables 9.4.2.2.3A/9.4.2.2.3B, page 136.
[a] Total number of hyperplasias calculated as number of patients with hyperplasia recorded by at least 2 pathologists.

Reviewer's Comments

The occurrence of 30 cases of endometrial hyperplasia, in a study population of 2,153 evaluable subjects after one year of study medication, is not unexpected, and is lower than the reported cases of endometrial hyperplasia in other large, controlled HRT clinical trials. The occurrence of one case of endometrial adenocarcinoma in a polyp in the 0.45 mg CE/1.5 mg MPA treatment group, and one case of endometrial adenocarcinoma in the 0.3 mg CE alone treatment group, in Study 0713D2-309-US do not present serious safety concerns. Furthermore, year 2 data from the

2-year osteoporosis and metabolic substudy for Study 0713D2-309-US presented no additional evidence of endometrial hyperplasia or cancer in any of the combination CE/MPA treatment groups.

Data presented in the submission demonstrates that the 0.3 mg CE/1.5 mg MPA dosage strength is successful in protecting the endometrium over the 2-years of treatment in the osteoporosis and metabolic substudy group in Study 0713D2-309-US.

Effects on Uterine Bleeding or Spotting

Bleeding profiles were summarized according to entries recorded by the subject in daily diary cards over the full two years in Study 0713D2-309-US. "Bleeding" was defined as vaginal bleeding requiring sanitary protection. "Spotting" was defined as vaginal bleeding that did not require sanitary protection. "Amenorrhea" was defined as the absence of any vaginal bleeding or spotting during the study period. In the submission, "no bleeding" was defined as the absence of vaginal bleeding regardless of the presence or absence of spotting.

Amenorrhea is the desired endpoint for the effects on uterine bleeding or spotting. The rate of cumulative amenorrhea over time is represented in labeling as the percentage of women in all treatment groups with no bleeding or spotting at a given month through month 12 for the intent-to-treat population using the LOCF approach.

In both Supplement-017 and Supplement-024, the incidence of amenorrhea was analyzed by using Fisher's exact test for pairwise comparisons in both the ITT and EE populations. EE subjects were defined as all subjects enrolled who had complete bleeding records (did not miss or fail to record ≥ 3 consecutive days or ≥ 5 nonconsecutive days of study medication per cycle) who completed 13 cycles/26 cycles. Two ITT populations were analyzed, ITT-1 and ITT-2. The ITT-1 population included all subjects enrolled in the study who recorded taking study medication. Any missing bleeding data were counted as bleeding. All days following a subject dropout were counted as bleeding. The ITT-2 population was defined similarly except all days following a subject dropout were counted as not bleeding.

Reviewer's comments

In NDA 20-527/S-017 and NDA 20-527/S-024 submissions, data is presented for both the EE and ITT population, which are differentiated according to whether or not 13 cycles/26 cycles were completed in the basic study/osteoporosis and metabolic substudy, respectively. However, it is customary in the Division to only utilize in labeling the ITT population data for calculating cumulative amenorrhea over 13 cycles of study medication. Therefore, like Supplement-017, the EE population analyses presented in this submission will not be discussed. Of the two ITT populations assessed, the more conservative ITT-1 population data (missing data and all days following dropout counted as bleeding) will be discussed. The data from study year 1 for the basic study group, which includes the osteoporosis and metabolic substudy group, presented in Supplement-017 over 13 cycles of study medication will be used in labeling.

In study year 1, the percentages of subjects in all treatment groups who became amenorrheic and remained so throughout the 13 cycles increased with each consecutive cycle. Overall, subjects in the CE-alone and CE/MPA treatment groups exhibited significantly fewer consecutive cycles of amenorrhea than subjects on placebo. However, only the 0.625 mg CE alone group (Group A) was significantly different from placebo at each analyzed time point.

Across the 8 treatment groups in study year 1, the percentage of subjects with consecutive cycles of amenorrhea for cycles 1 to 13 ranged from 16.6% (0.625/2.5, Group B) to 44.9% (placebo, Group H). See representation below. For cycles 7-13, the percentage of subjects with consecutive cycles of amenorrhea ranged from 31.6% (0.625 alone, Group A) to 53.3% (Placebo, Group H). At cycle 13, the

percentage of cumulative amenorrhea cycles ranged from 44.0% (0.625 alone, Group A) to 69.3% (Placebo, Group H). See year 1 Supportive Table 4 in Appendix A of this review.

At the start of treatment (cycles 1-13), all of the CE/MPA combination groups (except Group B) had significantly smaller percentages of subjects exhibiting consecutive cycles of amenorrhea versus the corresponding CE alone groups:

Group A vs. Group B		Group C vs. Group D or		Group E	Group F vs. Group G		Group H
0.625	0.625/2.5	0.45	0.45/2.5	0.45/1.5	0.3	0.3/1.5	Placebo
22.1%	16.6%	38.5%	25.6%	29.9%	43.9%	33.0%	44.9%

By cycles 7-13, similar percentages of subjects exhibited consecutive cycles of amenorrhea between the CE and CE/MPA combination treatment groups, especially Groups B:

Group A vs. Group B		Group C vs. Group D or		Group E	Group F vs. Group G		Group H
0.625	0.625/2.5	0.45	0.45/2.5	0.45/1.5	0.3	0.3/1.5	Placebo
31.6%	32.6%	50.6%	41.5%	42.3%	53.1%	46.6%	53.3%

By cycle 13, however, the percentages of subjects with amenorrhea in the CE/MPA groups were greater or near equal to that in the corresponding CE alone groups:

Group A vs. Group B		Group C vs. Group D or		Group E	Group F vs. Group G		Group H
0.625	0.625/2.5	0.45	0.45/2.5	0.45/1.5	0.3	0.3/1.5	Placebo
44.0%	62,2%	62.4%	66.2%	62.8%	67.8%	67.6%	69.3%

Reviewer's Comments

These findings are not unexpected. As the dosage strength of CE alone decreased the percentages of subjects with cumulative amenorrhea increased. In the active treatment groups (Groups A - G), the percentage of subjects exhibiting cumulative amenorrhea increased with decreasing dosages of CE. The highest CE alone dosage strength (0.625 mg) exhibited fewer cycles of cumulative amenorrhea than the 0.45 mg and 0.3 mg dosage strengths. The lowest CE alone dosage strength (0.3 mg) and placebo were not different at any time point analyzed.

At the start of treatment, all of the CE/MPA combination dosage strengths had significantly smaller percentages of subjects exhibiting consecutive cycles of amenorrhea versus the corresponding CE alone dosage strengths (22.1% vs. 16.6%; 38.5% vs. 25.6% and 43.9%; and 43.9% vs. 33.0%, respectively). By cycle 13, the lower dose CE/MPA dosage strengths (Groups D, E and G) had similar percentages of subjects with cumulative amenorrhea versus the corresponding CE alone dosage strengths (62.4% vs 62.2% and 62.8%; 67.8% vs. 67.6%, respectively), while Group B (0.625/2.5) was now higher than Group A (0.625). The 0.3 mg CE/1.5 mg MPA dosage strength and placebo were not different at cycle 13 (67.6% vs 69.3%).

In this submission, by cycle 13 in the osteoporosis and metabolic substudy group ITT-1 population (749 subjects), the percentages of substudy subjects with amenorrhea in the CE/MPA groups were greater than the corresponding CE alone groups:

Group A vs. Group B		Group C vs. Group D or		Group E	Group F vs. Group G		Group H
0.625	0.625/2.5	0.45	0.45/2.5	0.45/1.5	0.3	0.3/1.5	Placebo
53.6%	62.8%	58.9%	70.8%	60.6%	70.8%	69.4%	72.3%

By cycle 26 in the osteoporosis and metabolic substudy group ITT-1 population (595 subjects), the percentages of substudy subjects with amenorrhea in the CE/MPA groups continued to be greater than the corresponding CE alone group with the exception of the 0.45 mg CE/1.5 mg MPA group.

However, the result in the 0.45 mg CE/1.5 mg MPA treatment group (Group E) was similar to the result in the 0.625 mg CE/2.5 mg MPA treatment group (Group B):

Group A vs. Group B		Group C vs. Group D or Group E			Group F vs. Group G		Group H
0.625	0.625/2.5	0.45	0.45/2.5	0.45/1.5	0.3	0.3/1.5	Placebo
43.1%	60.0%	64.9%	74.7%	56.0%	71.2%	84.8%	80.0%

Reviewer's Comments

At cycle 13, the findings in the osteoporosis and metabolic substudy group alone were similar to the findings of the basic study group, which included the substudy subjects. In both groups of subjects, the highest CE alone dosage strength (0.625 mg) exhibited fewer cycles of cumulative amenorrhea than the 0.45 mg and 0.3 mg dosage strengths. Likewise, by cycle 13 in the osteoporosis and metabolic substudy, both the 0.45 mg CE/1.5 mg MPA and the 0.3 mg CE/1.5 mg MPA dosage strengths (Groups E and G) had similar percentages of subjects with cumulative amenorrhea versus the corresponding CE alone dosage strengths (60.6% vs. 58.9% and 69.4% vs. 70.8%, respectively).

However, by cycle 26, the findings in the osteoporosis and metabolic substudy group show that both the 0.625 mg CE/2.5 mg MPA (Group B) and the 0.3 mg CE/1.5 mg MPA (Group G) dosage strengths reported larger percentages of subjects with cumulative amenorrhea versus the corresponding CE alone dosage strengths (60.0% vs. 43.1% and 84.8% vs. 71.2%, respectively), while the 0.45 mg CE/1.5 mg MPA dosage strength (Group E) showed a slightly lower percentage of subjects with cumulative amenorrhea versus the corresponding CE alone dosage strength (56.0% vs. 64.9%).

Overall, for cycles 14 to 26 in year 2 of Study 0713D2-309-US, subjects in each active treatment group had fewer consecutive cycles of amenorrhea than subjects in the placebo treatment group with the exception of subjects in Group G (0.3 mg CE/1.5 mg MPA). By cycle 26, the 0.3 mg CE/1.5 mg MPA dosage strength ha a slightly higher percentage of subjects with consecutive cycles of amenorrhea than placebo (84.8% and 80.0%, respectively).

Data presented in the submission demonstrates that the 0.3 mgCE/1.5 mg MPA dosage strength exhibited a greater percentage of consecutive cycles of amenorrhea than the approved Prempro™ 2.5 at cycle 26.

6.4. Efficacy Conclusions

Data from a total of 241postmenopausal women in year 1 of the basic study group of the HOPE study was presented in the submission for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause. From the data presented in Study 0713D2-309-US, 0.3 mg CE/1.5 mg MPA taken daily, shows:

- a statistically significant reduction in the frequency and severity of hot flushes at weeks 4, 8, and 12 compared to placebo ($p<0.001$ at all time points);
- a statistically significant increase in the percentages of vaginal superficial cells from baseline at cycles 6 and 13 ($p<0.001$ at both time points), and a corresponding statistically significant decrease in the percentages of vaginal parabasal cells from baseline at cycles 6 and 13 ($p<0.001$ at all time points).

In addition, data from a total of 2,153 postmenopausal women with evaluable endometrial biopsies in year 1 of the basic study group, and 608 postmenopausal women with evaluable endometrial biopsies in the osteoporosis and metabolic substudy group in year 2 of the HOPE study was presented in the submission for protection of the endometrium. From the data presented, 0.3 mg CE/1.5 mg MPA taken daily, was effective in protecting the endometrium from equivalent estrogen-induced endometrial hyperplasia.

The reviewer recommends approval of the 0.3 mg CE/1.5 mg MPA dosage strength for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause, and protection of the endometrium.

7. INTEGRATED REVIEW OF SAFETY

7.1. Brief Statement of Conclusions

The safety data for 2-year Study 0713D2-309-US presented in the submission shows that the overall safety profile of 0.3 mg CE/1.5 mg MPA is acceptable. Higher doses of CE (0.625 mg) and MPA (2.5 mg and 5 mg) have been used in combination hormone replacement therapy since 1994.

Overall, the treatment emergent adverse event profile of the 0.3 mg CE/1.5 mg MPA dosage strength is similar to that of the currently approved products, Prempro™ 2.5, Prempro™ 5, and Premphase®.

7.2. Materials Utilized in the Review

The full two years of Study 0713D2-309-US was reviewed for safety outcomes. The safety population included all subjects who received at least one dose of study medication and had at least one follow-up safety evaluation. Safety findings for the completed but still blinded Study 0713D2312-JA were also reviewed.

7.3. Description of Patient Exposure

In year 1 of the HOPE study, a total of 2,673 subjects received treatment, 2,341 received treatment with CE alone or CE/MPA and 332 subjects received placebo. One thousand twelve (1,012) subjects received at least one dose of CE alone and 1,329 subjects received at least one dose of CE/MPA. See Table 7. All subjects who took study medication in the 1-year basic study and the 2-year osteoporosis and metabolic substudy are included in safety analyses except 48 subjects who received study medication at the terminated Study Site 30952. Study Site 30952 was terminated due to non-compliance with Good Clinical Practice. Eighty-one (81) subjects (25 of whom were in the substudy group) had no diary cards and therefore study medication intake could not be confirmed.

Table 7: Assessments of Exposure[a] to Active Medication in Year 1 of the HOPE Study

Parameter Days in Study	Group A 0.625[b] (n = 348)	Group B 0.625/2.5[b] (n = 331)	Group C 0.45[b] (n = 338)	Group D 0.45/2.5[b] (n = 340)	Group E 0.45/1.5[b] (n = 331)	Group F 0.3[b] (n = 326)	Group G 0.3/1.5[b] (n = 327)
Mean	309.1	329.8	326.2	323.5	328.7	326.5	329.8
SD[c]	107.6	93.3	88.1	95.6	89.4	90.7	84.7
Range	2-392	1-407	6-392	5-411	6-392	9-392	15-392

Source: Adapted from NDA 20-527/S-017, Volume 53, Table 10.1A, page 135.
[a] Values represent the maximum possible exposure to study medication.
[b] mg of CE or CE/MPA.
[c] SD = standard deviation.

In the substudy, a total of 655 of the 749 subjects were exposed to at least 1 dose of study medication. Two hundred eighty-one subjects were exposed to CE alone, 374 subjects were exposed to at least one dose of CE/MPA, and 94 subjects received at least one dose of placebo. Subjects in the osteoporosis and metabolic substudy were exposed to study medication over 26 cycles and are included in Table 7. Table 8 shows an assessment of exposure for only the substudy subjects over both years of the HOPE study.

Table 8: Assessments of Exposure[a] to Active Medication in Years 1 and 2 of the HOPE Study

Parameter Days in Study	Group A 0.625[b] (n = 97)	Group B 0.625/2.5[b] (n = 86)	Group C 0.45[b] (n = 95)	Group D 0.45/2.5[b] (n = 96)	Group E 0.45/1.5[b] (n = 94)	Group F 0.3[b] (n = 89)	Group G 0.3/1.5[b] (n = 98)
Mean	496.1	626.4	582.7	607	609.7	613.3	617.9
SD[c]	252.3	198.2	221.3	223.7	224	203.4	222.7
Range	28-756	1-742	41-757	42-758	7-756	82-756	28-756

Source: Adapted from NDA 20-527/S-024, Application Summary, Table 4.6.1A, page 160.
[a] Values represent the maximum possible exposure to study medication.
[b] mg of CE or CE/MPA.
[c] SD = standard deviation

7.4. Safety Findings from Clinical Studies

The postmenopausal use of estrogen/progestin combinations has been associated with an increased risk of breast cancer, cardiovascular events (myocardial infarction and stroke), venous thromboembolic events (deep vein thrombosis and pulmonary embolism), and gallbladder disease. Please see the Agency's 1992 Guidance for Industry entitled, "Labeling Guidance for Non-Contraceptive Estrogen Drug Products – Prescribing Information for Health Care Providers, and Patient Labeling" and the draft revision of the 1992 Guidance (**Federal Register**, Vol. 64, No. 186/Monday, September 27, 1999/Notices) for these and other labeled risks associated with the use of estrogen and estrogen/progestin drug products (see the **WARNINGS** and **PRECAUTIONS** sections). Please see the **CONTRAINDICATIONS** section for conditions for which estrogens and estrogen/progestin drug products should not be used. Revision of the Estrogen Class Labeling Guidance is ongoing.

Two recent published reports of controlled clinical trials have presented additional safety information for 0.625 mg CE/2.5 mg MPA (Prempro™ 2.5). Data from the Heart and Estrogen/progestin Replacement Study (HERS and HERS II), a controlled clinical trial of secondary prevention of 2,763 postmenopausal women with established coronary disease, showed that treatment for 6.8 years with 0.625 mg CE/2.5 mg MPA versus placebo in older women (average age of 67 years) with established coronary disease did not reduce the overall rate of coronary heart disease events, and increased rates of venous thromboembolism and biliary tract surgery.[1,2]

A subset of the Women's Health Initiative (WHI), a controlled primary prevention clinical trial of 16,608 primarily healthy postmenopausal women who received 0.625 mg CE/2.5 mg MPA versus placebo was stopped early (after an average of 5.2 years of a planned 8.5 years duration) because overall health risks exceeded benefits.[3] The reported absolute excess risks per 10,000 person-years attributable to 0.625 mg CE/2.5 mg MPA were 8 more cases of invasive breast cancers, 7 more coronary heart disease events, 8 more strokes, and 8 more cases of pulmonary embolism. The increased risk of breast cancer became apparent after 4 years of treatment. The increased risk of coronary heart disease was observed in year one and persisted. The increased risk of stroke was observed in year 2 and persisted. The increased risks of pulmonary embolism was observed during the first year and persisted. The reported absolute risk reductions per 10,000 person-years attributable to

[1] Grady D, Herrington D, Bittner V, et al, for the HERS Research Group. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA 2002 Jul 3;288(1):47-57.
[2] Hulley S, Furberg C, Barrett-Connor E, Cauley J, Grady D, et.al., Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA 2002 Jul 3;288(1):58-66
[3] Writing Group for the Women's Health Initiative Investigators. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women, Principal Results From The Women's Health Initiative Randomized Controlled Trial. JAMA 2002 July 17;288(3):321-333.

0.625 mg CE/2,5 mg MPA in the WHI were 6 fewer cases of colorectal cancers and 5 fewer hip fractures. The WHI clinical trial did not address the risks and benefits of estrogen/progestin given for the treatment of menopausal symptoms.

Deaths

Two deaths were reported during the 1-year basic study and none during the 2-year substudy. Subject 30921-0018, a 53 year old woman assigned to the 0.3 mg CE alone dosage strength (Group F) for 134 days, was diagnosed with adenocarcinoma of the lung following treatment for pneumonia and a persistent cough. She developed severe hypercalcemia, became comatose, and died of cardio-pulmonary failure. The event was considered to be unrelated to study medication by the investigator and medical monitor. Subject 30937-0129, a 50 year old woman assigned to the 0.45 mg CE/2.5 mg MPA dosage strength (Group D) for 217 days, was diagnosed with lung cancer (type unspecified) and died. The event was considered to be unrelated to study medication by the investigator and medical monitor.

Breast Cancer

A total of 8 breast cancers were reported in the NDA 20-527/S-017 at year 1. Seven cases of breast cancers occurred during treatment, and 1 case of breast cancer was reported approximately 1 year after study completion. One case of breast cancer was reported in each of the following four treatment groups: 0.625 mg CE alone, 0.625 mg CE/2.5 mg MPA, 0.45 mg CE/1.5 mg MPA (reported approximately 1 year post-study), and placebo. Four cases of breast cancer were reported in the 0.3 mg CE/1.5 mg MPA treatment group (Group G). No cases of breast cancer were reported in 0.45 mg CE alone, 0.45 mg CE/2.5 mg MPA, or 0.3 mg CE alone.

In addition to the 8 cases of breast cancer in study year 1, one subject (Subject 30919-0066 assigned to placebo) had a suspicious right mammogram at cycle 13. A mammotome biopsy showed lobular carcinoma in situ, multiple foci, with calcifications, cystic change, and apocrine metaplasia. This lesion is considered pre-cancerous.

In year 2 of the substudy, 3 subjects were reported to have breast cancer at cycle 26/27, and 1 subject had breast cancer reported post-study. One case of breast cancer was reported in each of the following treatment groups: 0.45 mg CE alone, 0.45 mg CE/1.5 mg MPA, 0.3 mg CE alone (reported approximately 9 months post-study), and placebo.

Please see Table 9 for a summary of the number of breast cancers reported in the HOPE study.

Table 9: Number of Cases of Breast Cancer in the 2-Year HOPE Study

	Year 1		Year 2		
Treatment	Cases	No. of Subjects	Cases	No. of Subjects[a]	Post-Study
0.625 mg CE	1	348	0	65	0
0.625 mg CE/2.5 mg MPA	1	331	0	75	0
0.45 mg CE	0	338	1	74	0
0.45 mg CE/2.5 mg MPA	0	340	0	79	0
0.45 mg CE/1.5 mg MPA	0	331	1	75	1[b]
0.3 mg CE	0	326	0	73	1[c]
0.3 mg CE/1.5 mg MPA	4	327	0	79	0
Placebo	1	332	1	75	0

Source: NDA 20-527/S-024, Application Summary, Table 5.3.1C, page 264.

[a] The population in year 2 consisted of those women in the substudy who continued into year 2.

[b] Diagnosed approximately 12 months after completing the 1-year study.

[c] Diagnosed approximately 9 months after completing the 2-year study.

Reviewer's Comments

In summary, of the 12 cases of breast cancer reported during the conduct of the 2-year HOPE study, 7 occurred during treatment in year 1, 3 occurred during treatment in year 2, and 2 were reported post-study. The placebo treatment group (2 cases of breast cancer), all three CE alone treatment groups (1 case of breast cancer each, total of 3), and 3 of the 4 combination CE/MPA treatment groups reported breast cancer (a total of 7 cases of breast cancer). In the combination CE/MPA treatment groups, one case of breast cancer occurred in the 0.625 mg CE/2.5 mg MPA treatment group, two cases of breast cancer occurred in the 0.45 mg CE/1.5 mg MPA treatment group, and 4 cases of breast cancer occurred in the 0.3 mg CE/1.5 mg MPA treatment group (all reported in year 1). Only the 0.45 mg CE/2.5 mg MPA treatment group was free of reported breast cancer.

Arterial Thromboses

There were 4 cases of arterial thrombosis reported in year 1 of Study 0713D2-309-US:

- Subject 30914-0055 was diagnosed with a transient ischemia attack (TIA) during cycle 5 of 0.45 mg CE/1.5 mg MPA treatment (considered to be unrelated to treatment per investigator).
- Subject 30931-0045 was diagnosed with a "stroke" during cycle 6 of treatment with 0.625 mg CE (considered to be unrelated to treatment per investigator).
- Subject 30940-0041, being treated with 0.625 mg CE/2.5 mg MPA, was diagnosed with a TIA on April 26, 1998 and discontinued medication. On May 21, 1998, she was diagnosed with left parietal subacute cerebral vascular accident (possibly related to study medication per investigator).
- Subject 30948-0045 was diagnosed with an acute inferior myocardial infarction during cycle 8 of placebo treatment (considered to be unrelated to treatment per investigator).

No cases of arterial thrombosis were reported in year 2 of Study 0713D2-309-US.

Reviewer's Comments

Arterial thromboses have been reported for the currently approved CE and CE/MPA drug products (Premarin®, Prempro™ 2.5, Prempro™ 5, and Premphase®).

There were four reported cases of arterial thrombosis in 2,673 treated subjects over 2 years in the HOPE study (three cases on active treatment and one case on placebo). Other large HRT clinical trials have reported similar or higher numbers of these events. Only one of the three reported cases of arterial thromboses on active treatment occurred in a lower CE/MPA dosage strength (1 TIA in the 0.45 mg CE/1.5 mg MPA dosage strength).

Venous Thromboembolic Events

Three (3) venous thromboembolic events were reported in year 1 of the HOPE study:

- Subject 30953-0031on 0.45 mg CE/1.5 mg MPA was diagnosed in cycle 9 of treatment with deep vein thrombosis of the left leg (possibly related to study medication per medical monitor).
- Subject 30963-0014 developed a blood clot in cycle 1 of treatment with 0.625 mg CE/2.5 mg MPA after being run over by a car (considered by the investigator to be possibly related to study medication).
- Subject 30965-0050 was diagnosed with a pulmonary embolism during cycle 9 of treatment with 0.45 mg CE (possibly related to study medication per medical monitor).

No cases of venous thrombosis were reported in year 2 of the HOPE study.

Reviewer's comments

There were two reported cases of deep vein thrombosis and one case of pulmonary embolism in 2,673 treated subjects over 2 years in the HOPE study. Deep vein thrombosis and pulmonary embolism are known to occur with CE and CE/MPA products approved for HRT.

Cholelithiasis

A total of seven (7) subjects developed cholelithiasis and/or cholecystitis while on study medication during years 1 and 2:

- Subject 30906-0050 during cycle 6 on 0.3 mg CE (possibly drug related).
- Subject 30911-0040 during cycle 1 on 0.3 mg CE/1.5 mg MPA (possibly drug related).
- Subject 30922-0006 during cycle 3 on 0.45 mg CE (unrelated per investigator/medical monitor).
- Subject 30938-0059 during cycle 3 on 0.45 mg CE/2.5 mg MPA (possibly related).
- Subject 30964-0068 during cycle 3 on 0.45 mg CE/2.5 mg MPA (possibly related).
- Subject 30965-0042 during cycle 14 (pancreatitis and cholelithiasis) on 0.3 mg CE/1.5 mg MPA (pancreatitis not related, cholelithiasis possible related).
- Subject 30918-0026 during cycle 15 on 0.45 mg CE/2.5 mg MPA (possibly related).

Six of the 7 subjects underwent cholecystectomy. Six of the 7 subjects continued in the study, one subject discontinue from the study prior to her cholecystectomy.

Reviewer's Comments

These numbers do not indicate a higher incidence of gallbladder disease and cholecystectomies with CE alone and CE/MPA combination therapy than reported in other HRT clinical trials.

Treatment Emergent Adverse Events

Eighty-nine percent (89%, n = 2,386) of the 2,673 treated subjects in the basic study group of Study 0713D2-309-US reported treatment-emergent adverse events (TEAE). In the 1-year study, the incidence of TEAEs in each age group (< 50, 50-59, 60 years of age or older) was comparable to that in the overall safety population: 89.6% of subjects in the 50 years of age group (n = 566), 89.3% in those subjects in the 50 to 59 year age group (n = 1,795), and 88.5% of those 60 years of age or older (n = 312). Please refer to the Medical Officer's Review of NDA 20-527/S-017, dated April 6, 2001, for a full description of treatment-emergent adverse events reported in year 1 of the HOPE study.

Ninety-six percent (96%, n = 718) of 749 substudy subjects in the 2-year substudy reported TEAEs. In the 2-year substudy, the incidence of TEAEs in the < 50 years of age and the 50 to 59 years of age subgroups was comparable with that in the overall safety population: 96% of subjects in the < 50 years of age group (n = 198) and 96% of those in the 50 to 59 years of age group (n = 532) reported any TEAEs. In those subjects 60 years of age and older (n = 19, number per treatment group ranged from 0 to 4), the percentages of subjects reporting any TEAEs ranged from 33% to 100%. There were no subjects in the 0.3 mg CE/1.5 mg MPA treatment group in this age group.

See Table 10 for the number and percent of subjects in the substudy group reporting ≥ 2% treatment-emergent adverse events in the 0.3 mg CE/1.5 mg MPA and placebo treatment groups.

Table 10: Number (%) of Subjects Reporting ≥ 2% Treatment Emergent Adverse Events in the PREMPRO 0.3/1.5 and Placebo Treatment Groups

Body System Adverse Event	0.3 mg CE/1.5 mg MPA (n = 98)	Placebo (n = 94)
Any Adverse Event	94 (96%)	87 (93%)
Body as a Whole		
Abdominal pain	17 (17%)	17 (18%)
Accidental injury	17 (17)	25 (27%)
Asthenia	4 (4%)	11 (12%)
Bach pain	25 (26%)	20 (21%)
Chest pain	3 (3%)	4 (4%)
Cyst	3 (3%)	5 (5%)
Fever	7 (7%)	3 (3%)
Flu Syndrome	21 (21%)	21 (22%)
Generalized edema	2 (2%)	4 (4%)
Headache	43 (44%)	35 (37%)
Infection	29 (30%)	33 (35%)
Neck pain	4(4%)	6 (6%)
Neck rigidity	2 (2%)	5 (5%)
Pain	30 (31%)	29 (31%)
Pelvic pain	2 (2%)	2 (2%)
Cardiovascular system		
Hypertension	5 (5%)	2 (2%)
Migraine	5 (5%)	2 (2%)
Palpitation	2 (2%)	0 (0%)
Digestive system		
Constipation	6 (6%)	9 (10%)
Diarrhea	9 (9%)	10 (11%)
Dyspepsia	17 (17%)	18 (19%)
Flatulence	8 (8%)	5 (5%)
Nausea	7 (7%)	11 (12%)
Periodontal abscess	5 (5%)	2 (2%)
Vomiting	3 (3%)	4 (4%)
Metabolic and nutritional		
Hypercholesteremia	4 (4%)	4 (4%)
Peripheral edema	0 (0%)	4 (4%)
Weight gain	4 (4%)	9 (10%)
Musculoskeletal System		
Arthralgia	15 (15%)	23 (24%0
Joint disorder	1 (1%)	5 (5%)
Leg cramps	8 (8%)	0 (0%)
Myalgia	11 (11%)	15 (16%)

Tenosynovitis	0 (0%)	7 (7%)
Nervous System		
Anxiety	8 (8%)	3 (3%)
Depression	7 (7%)	8 (9%)
Dizziness	7 (7%)	11 (12%)
Emotional lability	5 (5%)	5 (5%)
Hypertonia	1 (1%)	6 (6%)
Insomnia	8 (8%)	12 (13%)
Nervousness	4 (4%)	1 (1%)
Respiratory System		
Bronchitis	2 (2%)	5 (5%)
Cough increased	10 (10%)	5 (5%0
Pharyngitis	13 (13%)	16 (17%)
Rhinitis	19 (19%)	21 (22%)
Sinusitis	14 (14%)	7 (7%)
Upper respiratory infection	12 (12%)	15 (16%)
Skin and Appendages		
Contact dermatitis	2 (2%)	1 (1%0
Pruritis	5 (5%)	2 (2%)
Rash	1 (1%)	5 (5%)
Special Senses		
Ear disorder	2 (2%)	2 (2%)
Ear Pain	4 (4%)	8 (9%)
Urogenital System		
Breast disorder	2 (2%)	3 (3%)
Breast neoplasm	3 (3%)	2 (25)
Breast pain	17 (17%)	11 (12%)
Cervix disorder	3 (3%)	4 (4%)
Cystitis	6 (6%)	0 (0%)
Dysmenorrhea	5 (5%)	1 (1%)
Hematuria	1 (1%)	3 (3%)
Leukorrhea	4 (4%)	4 (4%)
Urinary tract infection	3 (3%)	8 (9%)
Uterine spasm	4 (4%)	3 (3%)
Vaginal dryness	0 (0%)	5 (5%)
Vaginal hemorrhage	2 (2%)	0 (0%)
Vaginal moniliasis	11 (11%)	5 (5%)
Vaginitis	5 (5%)	3 (3%)

Source: Adapted from NDA 20-527/S-024, Application Summary, Table 4.6.2.1A.

Reviewer's Comments

Serious adverse events reported during the 2 years of the HOPE study include 4 cases of arterial thrombosis (1myocardial infarction, 2 strokes, and 1 transient ischemic attack), 3 venous thromboembolic events (2 deep vein thrombosis and 1 pulmonary embolism), seven cases of cholelithiasis with cholecystectomy, and 12 cases of breast cancer (8 cases of breast cancer reported in year 1 and 4 cases of breast cancer reported in year 2).

As noted previously, breast cancer, cardiovascular disease, thromboembolic events and cholelithiasis with cholecystectomy are known to occur with estrogen alone and estrogen/progestin combination drug products and, overall, the incidence of these events in the HOPE study correlate with the findings in other large HRT clinical trials of similar treatment duration. However, the known risk for these adverse events, apparent from clinical trials of estrogen alone and estrogen/progestin combination drug products including the results of the Women's Health Initiative, warrant close post-marketing clinical surveillance.

Overall, treatment-emergent adverse events in the osteoporosis and metabolic substudy were similar between the 0.3 mg CE/1.5 mg MPA and placebo treatment groups. Headaches, infection and pain were the most frequently reported TEAE for both the 0.3 mg CE/1.5 mg MPA and placebo treatment groups (44% and 37% for headaches, 30% and 35% for infection, and 31% and 31% for pain, respectively). However, breast pain and vaginal hemorrhage (COSTART term that includes vaginal bleeding, intermittent vaginal bleeding, excessive or heavy vaginal bleeding) occurred more frequently in the 0.3 mg CE/1.5 mg MPA group than in the placebo group (17% and 2% compared with 12% and 0%, respectively). As previously noted, no cases of endometrial hyperplasia were reported in the 0.3 mg CE/1.5 mg MPA or placebo treatment groups in the substudy group.

Of clinical interest, however, is the number of subjects reporting breast pain across all 8 treatment groups in the substudy. For breast pain, a total of 13% of all subjects across the three CE alone treatment groups reported breast pain (37 of 281 substudy subjects). However, twice the number of subjects, 26%, reported breast pain across the four CE/MPA combination treatment groups (96 of 374 substudy subjects). Adding MPA to CE produced the following comparative breast pain results:

- **0.625 mg CE alone versus 0.625 mg CE/2.5 mg MPA = 14% versus 33%**
- **0.45 mg CE alone versus 0.45 mg CE/2.5 mg MPA = 13% versus 24%**
- **0.45 mg CE alone versus 0.45 mg CE/1.5 mg MPA = 13% versus 24%**
- **0.3 mg CE alone versus 0.3 mg CE/1.3 mg MPA = 11% versus 17 %**

Twelve percent (12%) of the placebo subjects reported breast pain (11 of 94 substudy subjects).

These findings demonstrate a statistically significant difference between CE alone and CE/MPA treatment groups ($p < 0.001$). In addition, a dose-dependent decrease in the percentage of subjects reporting breast pain is observed across the four CE/MPA combination treatment groups. The 0.3 mg CE/1.5 mg MPA dosage strength produced a lower incidence of breast pain than that observed in substudy subjects who received the approved Prempro™ 0.625/2.5 (17% and 33%, respectively. These findings are not unexpected, however.

Overall, the safety program for the 0.3 mg CE/1.5 mg MPA dosage strength is acceptable.

Safety-Related Discontinuations

A total of 266 out of 2,673 subjects (10%) in the basic study group (including the substudy subjects) discontinued from the study due to an adverse event during study year 1. Across all 8 treatment groups, discontinuations for any adverse event ranged from 6% for the 0.3 mg CE alone and placebo treatment groups (n=21 for both groups) to 21% for the 0.625 mg CE alone group (n=73). Nine percent

of subjects in each of three combination groups (0.65 mg CE/2.5 mg MPA, 0.45 mg CE/1.5 MPA, and 0.3 mg CE/1.5 mg MPA) withdrew for any adverse event (n=31, n=30, and n=30, respectively).

Twelve percent (12%, 43of 348 subjects) of subjects discontinuing in the 0.625 mg CE group reported endometrial hyperplasia and vaginal hemorrhage as the primary reasons for discontinuation. Vaginal hemorrhage alone, as a primary reason for discontinuation, was reported as follows:

CE alone groups:	0.625 mg = 9% (n=32 of 348 subjects)
	0.45 mg = 2% (n=6 of 338 subjects)
	0.3 mg = <1% (n=2 of 326 subjects)
CE/MPA groups:	0.625 mg/2.5 mg = 2% (n=8 of 331 subjects)
	0.45 mg/2.5 mg = 1% (n=4 of 340 subjects)
	0.45 mg/1.5 mg = 2% (n=8 of 331 subjects)
	0.3 mg/1.5 mg = < 1% (n=3 of 327 subjects)

No subjects in the placebo group discontinued because of vaginal hemorrhage or endometrial hyperplasia in the basic study group.

For the 2-year substudy group alone, 111 of 749 substudy subjects (15%) discontinued due to an adverse event. Similar to year 1 results, endometrial hyperplasia and vaginal hemorrhage were reported with the highest incidences: 2% with endometrial hyperplasia (16 of 749 substudy subjects, 10 subjects in the 0.625 mg CE alone treatment group and 6 subjects in the 0.45 mg alone treatment group) and 3% of substudy subjects with vaginal hemorrhage (20 of 749 substudy subjects). Vaginal hemorrhage alone, as a primary reason for discontinuation, was reported as follows for the substudy subjects:

CE alone groups:	0.625 mg = 11% (n=11 of 97 subjects)
	0.45 mg = 1% (n=1 of 95 subjects)
	0.3 mg = 1% (n=1 of 89 subjects)
CE/MPA groups:	0.625 mg/2.5 mg = 2% (n=2 of 86 subjects)
	0.45 mg/2.5 mg = 1% (n=1 of 96 subjects)
	0.45 mg/1.5 mg = 3% (n=3 of 94 subjects)
	0.3 mg/1.5 mg = 1% (n=1 of 98 subjects)

Reviewer's comments

Endometrial hyperplasia and vaginal hemorrhage are clearly associated with discontinuation among subjects assigned to the 0.625 mg CE alone treatment group in year 1 of Study 0713D2-309-US (basic study group) and across years 1 and 2 in the substudy group. The 0.3 mg CE/1.5 mg MPA dosage strength, however, produced the lowest incidence of discontinuations for both groups (< 1%, n = 3 of 327 basic study subjects, and 1%, n = 1 of 98 substudy subjects).

Overall, the number of discontinuations reported in Study 0713D2-309-US do not present safety-related concerns for this reviewer.

Metabolic Evaluations

A total of 749 of the subjects who were enrolled in Study 0713D2-309-US participated in the osteoporosis and metabolic substudy. The metabolic portion of the study included measurements on lipid and glucose/insulin metabolism and coagulation at baseline and cycles 6 and 13 for year 1 and cycles 19 and 26 for year 2. Please refer to the Medical Officer's review of NDA 20-527/S-017, dated April 6, 2001, for a full description of the metabolic findings reported in year 1 of the HOPE study.

Lipid Metabolism

Data for total cholesterol, HDL cholesterol, HDL_2 cholesterol, HDL_3 cholesterol, LDL cholesterol, VLDL-cholesterol, VLDL-triglycerides, and triglycerides were evaluated by analysis of variance

(ANOVA) based on the percent change from baseline at cycles 6, 13, 19, and 26. Data for lipoprotein (a) phenotype was collected at baseline only.

Four substudy subjects had noteworthy hypercholesteremia: Subjects 30964-0084 (0.45 mg CE/1.5 mg MPA) and 30906-0044 (Prempro™ 0.625/2.5) had elevated prestudy cholesterol levels that either remained elevated or increased throughout the 2-year study; Subject 30906-0050 in the 0.3 mg CE alone treatment group had elevated cholesterol levels during cycles 13, 19, and 26 that persisted after study completion; and Subject 30907-0051 in the Prempro™ 0.625/2.5 treatment group had elevated cholesterol and triglyceride levels throughout the study that persisted after study completion. All four events were judged to be probably/possibly drug related.

Mean percent changes from baseline after 6, 13, 19, and 26 cycles are as follows:

Total cholesterol	- During the first year of treatment of the 0.625 mg and 0.45 mg CE treatment groups, with and without MPA, there was a mean percent decrease in total cholesterol concentrations ranging from 0.22% to 4.58%. During the second year of treatment, the mean percent change from baseline was similar, ranging from –2.73% to +2.08%. - During 2 years of treatment with 0.3 mg CE alone or with 1.5 mg MPA, the mean percent change from baseline ranged from –0.44% to +2.90%. - During 2 years of treatment with placebo there was a mean percent increase of 1.34% to 5.68%.
HDL-cholesterol	- During 2 years of treatment, all active treatment groups had statistically significant mean percent increases in HDL cholesterol, ranging from 5% to 20%, which were greater than the 2% to 4% mean percent increases that occurred with placebo. - The mean percent increase in the 0.3 mg CE/1.5 mg MPA group was statistically significantly greater than placebo at cycle 19 (p=0.049).
HDL_2-cholesterol	- During 2 years of treatment, all active treatment groups treated with CE, with or without MPA, showed statistically significant mean percent increases in HDL_2 cholesterol, compared with no significant change in the placebo treatment group. - The mean percent increases from baseline HDL_2-C were statistically significant at cycles 6 and 26 for the 0.3 mg/1.5 mg CE/MPA group (p=0.14 and p=0.035, respectively).
HDL_3-cholesterol	- During 2 years of treatment, mean percent increases of less than 10% from baseline were statistically significant in all active-treatment groups at most time points. - The mean percent increase in HDL_3-cholesterol in the 0.3 mg CE/1.5 mg MPA treatment group were similar with placebo.
LDL-cholesterol	- During 2 years of treatment, the mean percent decreases in LDL cholesterol were significantly greater with all active treatment than with placebo. - There was no difference in mean percent decreases in LDL cholesterol in CE and comparable CE/MPA groups. - The mean percent decreases in LDL cholesterol were statistically significant in the 0.3 mg CE/1.5 mg MPA treatment group at cycles 6 and 19
VLDL-cholesterol	-During 2 years of treatment, the mean percent increases in VLDL-cholesterol were statistically significant in the 0.3 mg CE/1.5 mg MPA treatment group at cycles 6, 13, and 19. - There were no statistically significant differences between placebo and any dose of CE with or without MPA.
VLDL-triglycerides	- During 2 years of treatment, there were statistically significant mean percent increases in VLDL-triglycerides in all active-treatment groups at cycles 6, 13, 19, and 26 with the exception of the 0.3 mg CE alone and the 0.45 mgCE/1.5 mg MPA treatment groups at cycle 26.

	- Most increases with active treatments were not significantly different from those with placebo.
Triglycerides	- During 2 years of treatment, the mean percent increase from baseline triglyceride levels were statistically significant in the 0.3 mg CE/1.5 mg MPA treatment group at cycles 6, 13, 19, 26. - The mean percent increase from baseline triglyceride levels for the 0.3 mg CE/1.5 mg MPA treatment group was not significantly different from placebo at any cycle.

Reviewer's Comments

All active-treatment groups, including the 0.3 mg CE/1.5 mg MPA treatment group, showed favorable increases in HDL-cholesterol (cycle 19 for the 0.3 mg CE/1.5 mg MPA treatment group) and HDL_2-cholesterol (cycles 6 and 26 for the 0.3 mg CE/1.5 mg MPA treatment group), as opposed to the small changes seen in the placebo treatment group. All active-treatment groups showed favorable decreases in LDL-cholesterol at most or all cycles (statistically significant difference between the 0.3 mg CE/1.5 mg MPA group and placebo at all cycles), while the placebo treatment group showed significant increases at cycles 13, 19, and 26.

Overall, these findings show a favorable lipid profile for the 0.3 mg CE/1.5 mg MPA treatment dosage strength.

Carbohydrate Metabolism

In the 2-year substudy subjects, the glucose and insulin results from 3-hour GTTs were similar to pretreatment values for all active treatment groups and placebo at cycles 6, 13, 19, and 26. Occasional sporadic mean percent changes from baseline values in the glucose and insulin concentrations were seen at various times during the GTTs. In the 1 year interim data submitted in NDA 20-527/S-017, Subject 30958-0035 (52 years of age assigned to the 0.3 mg CE/1.5 mg MPA treatment group) had elevated glucose levels and elevated GTT results at cycle 6, which resulted in a diagnosis of type II diabetes mellitus.

Reviewer's Comments

Overall, in the 2-year substudy, the decreases and increases in glucose and insulin concentrations following glucose challenge did not result in any treatment-related changes in glucose tolerance or the development of insulin resistance.

Coagulation Factors

In the substudy data submitted, there were some statistically significant increases and decreases from baseline values in clotting times, procoagulant factors, and anticoagulant factors:

- Occasional slight sporadic decreases from baseline prothrombin time values and differences between all active-treatment group and the placebo group were noted but were not considered to be clinically important. There were no statistically significant changes in prothrombin time between subjects receiving CE alone and CE/MPA combination groups.
- Slight but statistically significant changes from baseline partial thromboplastin time ranged from a mean of 2.12 seconds to a mean decrease of 0.86 seconds in all active-treatment groups and were similar to the placebo treatment group.
- A significant difference in the adjusted mean change from baseline in the partial thromboplastin time ratio was noted between the 0.3 mg CE/1.5 mg MPA treatment group and placebo. However, these changes are not considered to be clinically important.
- During cycles 6 and 13 of treatment, there were no statistically significant mean changes from baseline values in factor VIII activity with placebo or any active-treatment group except for a slight increase in the 0.3 mg CE/1.5 mg MPA group. However, a slight mean decrease in factor VIII activity

in all active-treatment groups, with no difference in the placebo group, was noted during cycles 19 and 26.

- A slight but statistically significant mean decrease from baseline fibrinogen activity in all active-treatment groups except the 0.3 mg CE/1.5 mg MPA and placebo treatment groups was noted during cycles 6 and 13. Mean increases from baseline fibrinogen activity were significant for the placebo group during cycles 19 and 26.
- Statistically significant mean increases in plasminogen activity were seen in all active-treatment groups at all time points but only during cycle 13 for the placebo treatment group. There were no significant differences in plasminogen activity between CE alone and the comparable CE/MPA treatment groups at any time points.
- There were statistically significant decreases from baseline PAI-1 (plasminogen activator inhibitor) activity in all active-treatment groups except in the 0.3 mg CE/1.5 mg MPA treatment group during cycles 13 and 26 and in the 0.45 mg CE/2.5 mg MPA treatment group during cycles 6 and 26.
- Slight but statistically different mean decreases in antithrombin III activity were seen in all active treatment groups except the 0.3 mg CE/1.5 mg MPA treatment group during cycle 13 and during cycles 6, 13, and 19 for the placebo treatment group. There were no significant differences in antithrombin III activity between CE alone and comparable CE/MPA treatment groups during any cycle.
- Sporadic small but statistically significant mean increases and decreases from baseline concentrations of protein C were noted. Three subjects who received 0.3 mg CE/1.5 mg MPA and one subject who received 0.3 mg CE alone were found to have lower than normal protein C in baseline and on-treatment samples.
- Statistically significant decreases in protein S activity occurred in women in all active-treatment groups except the 0.3 mg CE/1.5 mg MPA and placebo groups.

Reviewer's Comments

The substudy results show some statistically significant increases and decreases from baseline values in factors known to affect hemostatic balance. However, no consistent changes in clotting times and in procoagulant, fibrinolytic, and anticoagulant factors were noted.

7.5. Miscellaneous Studies

Safety information from one non-IND study conducted in Japan (Study 0713D2-312-JA) was included in NDA 20-527/S-024 (study ongoing at the time of the S-024 submission) and the 4-Month Safety Update (Study 0713D2-312-JA now completed but treatment assignments remain blinded). Study 0713D2-312-JA is a 52-week double-blind, double-dummy, multicenter study conducted in Japan that randomized approximately 360 postmenopausal women to receive 2 doses of CE/MPA (0.625 mg CE/2.5 mg MPA and 0.3 mg CE/1.5 mg MPA) and 2 mg Estriol for the prevention of postmenopausal osteoporosis.

7.6. Literature Review for Safety

No independent literature review was conducted.

7.7. Postmarketing Surveillance – If Applicable

The Global Safety Surveillance and Epidemiology (GSSE) database is maintained by the Sponsor to identify spontaneously reported events from postmarketing exposure, as well as serious adverse drug events from any clinical trials.

The currently approved Prempro™ 2.5, Prempro™ 5, and Premphase® are marketed worldwide. A combination package of Premarin® with MPA is registered in 72 countries worldwide.

7.8. Safety Update

4-Month Safety Update

The 4-Month Safety Update includes serious adverse events not previously reported for Study 0713D2-309-US from April 1, 2001 through January 31, 2002, and for Study 0713D2-312-JA from December 31, 2000 through January 31, 2002.

For Study 0713D2-309-US, one follow-up to a serious adverse event reported for Subject 30939-0117 revealed a discrepancy in the notation of drug relationship. A pre-cancerous lobular carcinoma in situ for Subject 30939-0117 was reported as considered not drug-related by both the investigator and the medical monitor. When the database was finalized, it was noted that the investigator, but not the medical monitor, had considered the event to be possibly drug-related.

For non-IND Study 0713D2-312-JA, the assignment to treatment remains blinded. As of January 31, 2002, fifteen of 360 subjects reported serious adverse events. All 15 subjects were hospitalized. Of the 15 serious adverse events reported: 7 were due to orthopedic problems/injuries, 3 were due to cancer (one cancer each = colon, endometrial, and breast); other diagnoses include extraction of wisdom tooth (1), gastric/colon polyp (1), neuroparalysis (1), suspected endometrial hyperplasia (1), and abdominal pain (1).

One initial 15-day report for ischemic colitis was filed to IND 21,696 (Serial Number 219) for Subject 30912-0015 (0.45 mg CE/1.5 mg MPA) in Study 0713D2-309-US (originally thought to be taking placebo). In addition, one follow-up report was submitted to IND 21,696 for Subject 30914-0055 (0.45 mg CE alone, transient ischemic attack, Serial Number 220) for the reporting period from April 1, 2001 through January 31, 2002.

Reviewer's Comments

The serious adverse events reported in the 4-Month Safety Update are not unexpected for postmenopausal women receiving hormone replacement therapy.

7.9. Drug Withdrawal, Abuse, and Overdose Experience

No serious adverse events were reported as a result of 0.3 mg CE/1.5 mg MPA abuse or overdose during the conduct of the HOPE study. Overdosage of estrogens may cause nausea and vomiting, and withdrawal bleeding in postmenopausal women with a uterus.

7.10. Adequacy of Safety Testing

Prestudy safety assessments were appropriate for the 2-year study. These safety assessments included a complete physical examination including a pelvic examination with a Pap smear, vaginal Maturation Index, and an endometrial biopsy. A prestudy mammogram was performed unless a written, normal report of a mammogram performed within the pervious 6 months was available (current HRT Guidance reduces the acceptable interval to 3 months). A laboratory safety screen was done after a minimum 12-hour fast and included hematologic and blood chemistry tests, urinalysis, and serum FSH and estradiol concentrations were performed. In the substudy group of subjects, additional laboratory assessments were performed including lipid profiles, carbohydrate and coagulation procedures, thyroid stimulating hormone (TSH) and Lp(a) phenotype, and bone markers (serum osteocalcin and urinary calcium, creatinine, and N-telopeptide). In substudy subjects, lipid profiles were assessed twice before treatment, 7 to 14 days apart.

All study subjects were evaluated during cycles 3, 6, 9, and 13. Substudy subjects that continued for year 2 had additional evaluations performed at cycles 16, 19, 22, and 26. The procedures and laboratory tests performed during cycles 1 to 14 in year 1, and for cycles 15 to 26 in year 2, are appropriate. Per the study protocol, endometrial biopsies were routinely performed at cycles 6 and 13

during study year 1, and cycles 19 and 26 of study year 2. Endometrial biopsies were obtained during cycle days 15 to 28. Mammograms were repeated at cycles 13 and 26 for all study subjects.

7.11. Labeling Safety Issues and Postmarketing Commitments

The proposed labeling for Prempro™/Premphase® complies with the labeling guidance for estrogen drug products.

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

Prempro™ 2.5, Prempro™ 5, and Premphase® are approved for continuous oral administration, one tablet daily. Daily continuous oral administration of 0.3 mg CE/1.5 mg MPA is recommended.

In the proposed labeling, the Sponsor lists three dosage strengths of Prempro™ (Prempro™ 0.3/1.5, Prempro™ 0.625/2.5, and Prempro™ 0.625/5) and Premphase® for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy with the notation that "patients should be started at the lowest effective dose" and that in patients "where bleeding or spotting remains a problem, after appropriate evaluation, consideration should be given to increasing the dose."

Reviewer's Comments

The findings presented in NDA 20-527/S-017 and NDA 20-527/S-024 confirms that the 0.3 mg CE/1.5 mg MPA dosage strength is safe and effective for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause. Therefore, labeling should indicate that Prempro™ 0.3/1.5 is the lowest effective dose for these indications.

9. USE IN SPECIAL POPULATIONS

9.1. Evaluation of Applicant's Efficacy and Safety Analyses of Effects of Gender, Age, Race, or Ethnicity. Comment on Adequacy of Applicant's Analyses.

Prempro™ is indicated for use in postmenopausal women with a uterus. Prempro™ is not indicated for use in a pediatric population.

Please refer to the Medical Officer's review of NDA 20-527/S-017, dated April 6, 2001, for a full description of the effects of age, race, or ethnicity reported for the basic study group in year 1 of the HOPE study.

9.2. Pediatric Program (e.g., pediatric waivers, deferrals, written requests)

A request for a pediatric waiver was submitted with NDA 20-527/S-024 on November 5, 2001. Prempro™ 0.3/1.5 is only recommended for use in postmenopausal women.

9.3. Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy.

The 0.3 mg CE/1.5 mg MPA dosage strength was investigated in postmenopausal women. No data is available for other special populations. Prempro™ 0.3 mg CE/1.5 mg MPA should not be used during pregnancy.

10. CONCLUSIONS AND RECOMMENDATIONS, AND LABELING

10.1. Conclusions Regarding Safety and Efficacy

The safety and efficacy data, presented in NDA 20-527/S-024, is adequate to support the approval of the 0.3 mg CE/1.5 mg MPA dosage strength for the treatment of vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause in women with a uterus, and protection of the endometrium.

10.2. Recommendations on Approvability

The data presented in this supplemental NDA provides sufficient evidence from one large, placebo-controlled clinical trial (Study 0713D2-309-US) to support the safety and efficacy of 0.3 mg CE/1.5 mg MPA taken daily for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause, and the protection of the endometrium. From a clinical perspective, the 0.3 mg CE/1.5 mg MPA dosage strength can be approved.

10.3 Labeling

The proposed labeling submitted was modified in accordance with the proposed revisions to the "Labeling Guidance for Noncontraceptive Estrogen Drug Products – Prescribing Information for Healthcare Providers and Patient Labeling" as published in the **Federal Register**, Vol. 64, No. 186, September 27, 1999, Notices. In addition, the proposed labeling was revised to include information adapted from the Women's Health Initiative study as reported in JAMA, July 17, 2002, Volume 288, Number 3, pages 321-333.

Four dosage strengths are listed under the **DESCRIPTION** section: Prempro™ 0.3/1.5, Prempro™ 0.625/2.5, Prempro™ 0.625/5, and Premphase®.

Revisions have been made to the **CLINICAL PHARMACOLOGY** section under the **Pharmacokinetics** subsections to update the text and to add the following information under the **Drug Interactions** subsection:

"Data from a single dose drug-drug interaction study involving conjugated estrogens and medroxyprogesterone acetate indicate that the pharmacokinetic disposition of both drugs are not altered when the drugs are coadministered. No other clinical drug-drug interaction studies have been conducted with conjugated estrogens.

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects."

The following revisions have been made to the **Clinical Studies** subsection:

- Minor revisions under the ***Effects on vasomotor symptoms*** and ***Effects on vulvar and vaginal atrophy*** subsections.
- Table 5 has been revised under the ***Effects on the endometrium*** subsection. The table has been retitled to read, "Incidence Of Endometrial Hyperplasia Or Cancer After One Year Of Treatment." Line three has been modified to read, "hyperplasia/cancer" and the reported numbers have been adjusted. The results of pathologists 1 and 2 have been deleted.
- Under the ***Effects on uterine bleeding or spotting*** subsection, the Sponsor has been requested to renumber the figures. The renumbered Figures 1 and 2 have been retitle, "Patients With Cumulative Amenorrhea Over Time (Percentages of Women With No Bleeding Or Spotting At A Given Cycle Through Cycle 13), Intent-to-Treat Population". The sponsor has been requested to delete the other two figures that pertain to all patients who complete 13 cycles.

- A subsection entitled, "***Effects on bone mineral density***" has been added. The added text is the same as included in Supplement –017 that received an Approvable action on April 13, 2001.
- A subsection entitled, "***Women's Health Initiative Studies***" has been added. The following information is included:

"A subset of the Women's Health Initiative (WHI) enrolled 16,608 predominantly healthy postmenopausal women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic) to assess the risks and benefits of long-term use of PREMPRO (0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate per day) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of PREMPRO on menopausal symptoms. The PREMPRO subset was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified long-term benefits included in the "global index". Results are presented in Table 10 below:

Table 10. RELATIVE AND ABSOLUTE RISK SEEN IN THE PREMPRO SUBSET 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 **WARNINGS** and **PRECAUTIONS**.)"

The following information has been added under **INDICATIONS AND USAGE**:

(b) (4)

Under the **CONTRAINDICATIONS** section, the listed contraindications have been revised and reordered, and the following contraindication has been added, "Active or recent arterial thromboembolic disease (eg, stroke, myocardial infarction)."

Under the **WARNINGS** heading, the following information has been added:

(b) (4)

The section has been revised to read as follows:

"**1. Cardiovascular Disorders.**

(b) (4)

a. Coronary heart disease and stroke. In the PREMPRO subset of the Women's Health Initiative study (WHI), an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving PREMPRO compared to women receiving placebo (37 vs 30 per 10,000 person-years). The increase in risk was observed in year one and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In the same subset of WHI, an increased risk of stroke was observed in women receiving PREMPRO compared to women receiving placebo (29 vs 21 per 10,000 person-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/progestin Replacement Study; HERS) treatment with PREMPRO (0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with PREMPRO did not reduce the

overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the PREMPRO-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the PREMPRO group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. Venous thromboembolism (VTE). In the PREMPRO subset of WHI a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving PREMPRO compared to women receiving placebo. The rate of VTE was 34 per 10,000 woman-years in the PREMPRO group compared to 16 per 10,000 woman-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant Neoplasms.

a. Breast cancer. (b) (4)

b. Endometrial cancer. The reported endometrial cancer risk among users of unopposed estrogen was about 2- to 12-fold greater than in nonusers and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose.

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported in a large clinical trial to occur at a rate of approximately 1% or less with PREMPRO or PREMPHASE. In this large clinical trial, only a single case of endometrial cancer was reported to occur among women taking combination Premarin/medroxyprogesterone acetate therapy.

(b) (4)

Revised language has also been recommended for the following subsections, **Gallbladder Disease**, **Hypercalcemia,** and **Visual Abnormalities**.

In the **PRECAUTIONS** section, revised language is recommended as follows:

"A. General
1. ***Addition of a progestin when a woman has not had a hysterectomy.***
Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins in postmenopausal hormone therapy regimens compared to estrogen-alone regimens. These include an increased risk of breast cancer (see **WARNINGS, Malignant neoplasms**), adverse effects on lipoprotein metabolism (eg, lowering HDL, raising LDL) and impairment of glucose tolerance.

2. ***Elevated blood pressure.***
In a small number of case reports, substantial increases in blood pressure during postmenopausal estrogen therapy have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

3. ***Familial hyperlipoproteinemia.***
In patients with familial defects of lipoprotein metabolism, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

4. ***Impaired liver function and past history of cholestatic jaundice.***

Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

5. ***Hypothyroidism.***
Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. ***Fluid retention.***
Because estrogens/progestins may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

7. ***Hypocalcemia.***
Estrogens should be used with caution in individuals with severe hypocalcemia.

8. ***Exacerbation of endometriosis.***
Endometriosis may be exacerbated with administration of estrogen therapy.

9. ***Exacerbation of other conditions.***
Postmenopausal estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria and should be used with caution in women with these conditions."

In the **ADVERSE REACTIONS** section, the Sponsor is requested to replace Tables 11 and 12 with tables that show adverse events with ≥ 2% occurrence rate. All references found under the phrase, "additional adverse reactions have been reported with estrogen/progestin therapy" have been deleted.

Under the **DOSAGE AND ADMINISTRATION** section, for the treatment of moderate-to-severe vasomotor symptoms indication, the text has been revised to indicate that patients should be started at PREMPRO 0.3/1.5 daily.

The **PATIENT INFORMATION** insert has been modified in compliance with the plain language initiative and recommendations from the Division of Drug Marketing, advertising and Communications (DDMAC), and the Division of Surveillance, Research & Communication Support (DSRCS).

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

/s/

Theresa Van Der Vlugt
8/28/02 11:18:32 AM
MEDICAL OFFICER

Shelley Slaughter
8/28/02 01:07:14 PM
MEDICAL OFFICER
I concur.

Prempro™ Team Leader Review

NDA:	**20-527, S-024**
Drug:	**Prempro™**
Claim:	**Protection of the endometrium from the development of estrogen-induced endometrial hyperplasia or cancer**
Proposed Indications:	**1. Treatment of moderate-to-severe vasomotor symptoms** **2. Treatment of vulvar and vaginal atrophy**
Dosage/Form/Route:	**0.30 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate via oral tablet**
Applicant:	**Wyeth-Ayerst Research**
Original Submission Date:	**November 5, 2001**
Receipt Date:	**November 7, 2001**
Primary Review Completed:	**August 22, 2002**
Date of Memorandum:	**August 23, 2002**

Background and Regulatory History

Wyeth-Ayerst received approval for NDA 20-303 on December 30, 1994 to market Prempro™ and Premphase®, two oral combination drug products consisting of conjugated estrogens (CE) and medroxyprogesterone acetate (MPA). One dosage strength was approved, Prempro™2.5 (0.625 mg CE/2.5 mg MPA). Initially, Prempro™2.5 and Premphase® were co-packaged products. Prempro™ consisted of one tablet of CE and one tablet of MPA taken on a continuous daily basis and Premphase® consisted of one tablet of CE taken on days 1-14 of the month and one tablet of CE and one tablet of MPA taken on days 15-28 of the month. On November 17, 1995, the Agency approved NDA 20-527 for Prempro™ 2.5, a single tablet of 0.625 mg CE/2.5 mg MPA taken on a continuous daily basis and Premphase®, a single tablet of CE taken for days 1-14 of the month and single tablet of 0.625 mg CE/2.5 mg MPA taken for days 15-28 of the month. NDA 20-527, supplement 006 for Prempro™ 5 (0.625 mg CE/5 mg MPA in a single tablet taken on a continuous daily basis) was approved on January 9, 1998. Prempro™ 2.5, Prempro™ 5, and Premphase® are all approved for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause (VMS) in women with a uterus, treatment of vulvar and vaginal atrophy associated with the menopause (VVA) in women with a uterus, and prevention of postmenopausal osteoporosis.

With the initial approval of Prempro™ and Premphase®, the Agency requested from Wyeth-Ayerst a Phase 4 commitment to investigate the lowest dose combination of CE and MPA for the prevention of postmenopausal osteoporosis. On June 5, 2000, Wyeth-Ayerst submitted NDA 20-527, supplement 017 (S-017) that presented the year 1 interim analyses of efficacy and safety data from Study 0713D2-309-US on the 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/ 1.5 mg MPA dosage strengths for VMS, VVA, and protection of the endometrium. Study 0713D2-309-US was a controlled clinical trial conducted to satisfy the post-approval Phase 4 commitment. No data was presented regarding the prevention of postmenopausal osteoporosis. The unblinding

strategy to assemble and analyze the interim data for S-017 while preserving the integrity of the ongoing study was presented to the Agency on December 9, 1999. The Agency concurred with the proposed unblinding procedures on December 16, 1999. Year 2 of Study 0713D2-309-US was ongoing at the time of submission of S-017. On April 3, 2001, the Sponsor withdrew the 0.3 mg CE/ 1.5 mg MPA dosage strength for consideration of approval. On April 13, 2001, Prempro™ 0.45 mg CE/1.5 mg MPA received an Approvable action from the Agency for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause. The claim of protection of the endometrium for Prempro™ 0.45 mg CE/1.5 mg MPA was also supported by the data submitted in S-017. NDA 21-396 for the indication of prevention of postmenopausal osteoporosis for Prempro™ 0.45 mg CE/1.5 mg MPA and Prempro™ 0.30 mg CE/1.5 mg MPA received an Approvable action on July 25, 2002.

The Sponsor submitted on November 5, 2001, NDA 20-527/S-024 (S-024) for Prempro™ 0.30 mg CE/1.5 mg MPA for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy. S-024 was filed on January 7, 2002.

Clinical

Study 0713D2-309-US, the Health and Osteoporosis, Progestin and Estrogen (HOPE) study was a 2 year prospective, multi-center, double-blind, randomized, parallel-group active- and placebo-controlled Phase 3 study. Each study subject took both an active drug and placebo control tablet except those subjects randomized to the placebo group who took two placebo tablets. In addition to the study medication, all study subjects received 1 tablet of Caltrate®, 600 mg elemental calcium. Two thousand eight hundred five (2,805) subjects were randomized into 8 treatment groups. Of these 2,805 subjects randomized, 132 subjects do not appear in the analyses. Eighty-one (81) subjects provided no medication use data and 51 subjects were excluded by the Sponsor (the clinical review team concurs) from the efficacy analyses because they participated at a Clinical Site (30952) that was terminated because of noncompliance with Good Clinical Practice. Two thousand six hundred seventy three (2,673) women took medication and were included in the efficacy analysis. The numbers of subjects per treatment group included in the efficacy analyses are as follows:

Group A: 0.625 mg CE – 348 subjects
Group B: 0.625 mg CE/2.5 mg MPA – 331 subjects
Group C: 0.45 mg CE – 338 subjects
Group D: 0.45 mg CE/2.5 mg MPA – 340 subjects
Group E: 0.45 mg CE/1.5 mg MPA – 331 subjects
Group F: 0.3 mg CE – 326 subjects
Group G 0.3 mg CE/1.5 mg MPA – 327 subjects
Placebo- 332 subjects

As indicated above, the Agency agreed with the plan to perform interim analyses of the data for VMS, VVA and protection of the endometrium. Only 9% (241) of the 2,673 treated subjects met the 1995 Guidance for Clinical Evaluation Of Combination Estrogen/Progestin-Containing Drug Products Used For Hormone Replacement Therapy of Postmenopausal Women (HRT Guidance)– specified number of moderate-to-severe vasomotor symptoms (7-8 per day or 50-60 per week) to be enrolled in a study to assess VMS. The 241 subjects who met the enrollment requirements were equally divided between the 8 treatment groups (ranging between 27 to 34 subjects per group). The Sponsor's original efficacy analysis for VMS utilized a baseline adjusted mean value and did not include last observation carried forward (LOCF). For consistency (with regard to the

Label), the Sponsor was asked to provide efficacy analysis with the mean change and not baseline adjusted mean and to impute missing data with a LOCF approach. The efficacy analyses for those subjects meeting the requisite number of moderate-to-severe vasomotor symptoms (MSVS) are presented in Tables 1 and 2 which are modified from the medical officer's (MO) Tables 2 and 3.

Table 1: Mean Daily Number of Moderate-to-Severe Hot Flushes and Change from Baseline in Mean Daily Number of Moderate-to-Severe Hot Flushes during Therapy in All Subjects with ≥ 7 Moderate-to-Severe Hot Flushes Per Day at Baseline, Intent-to-Treat Population with LOCF[a]

Week	0.3 mg CE/1.5 mg MPA n=33	Placebo n=28
Baseline		
Mean Number	11.30	11.69
Week 4		
Mean Number	4.01	8.09
Mean Change[b]	-7.60	-3.80
p-value vs. placebo[c]	<0.001	N/A
Week 8		
Mean Number	2.63	6.93
Mean Change[b]	-8.84	-4.86
p-value vs. placebo[c]	<0.001	N/A
Week 12		
Mean Number	1.47	5.81
Mean Change[b]	-10.00	-5.98
p-value vs. placebo[c]	<0.001	N/A

[a]LOCF = last observation carried forward
[b]Mean change from baseline
[c]p-value is based on analysis of covariance with treatment as factor and baseline as covariate

Table 2. Mean Daily Severity and Change from Baseline in the Mean Daily Severity of Hot Flushes during Therapy in All Subjects with ≥ 7 Moderate-to-Severe Hot Flushes Per Day at Baseline, Intent-to-Treat Population with LOCF[a]

Week	0.3 mg CE/1.5 mg MPA n=33	Placebo n=28
Baseline		
Mean Severity	2.24	2.37
Week 4		
Mean Severity	1.48	2.03
Mean Change[b]	-0.79	-0.29
p-value vs. placebo[c]	<0.001	N/A
Week 8		
Mean Severity	0.93	1.76
Mean Change[b]	-1.34	-0.57
p-value vs. placebo[c]	<0.001	N/A
Week 12		
Mean Severity	0.58	1.62
Mean Change[b]	-1.67	--0.72
p-value vs. placebo[c]	<0.001	N/A

[a]LOCF = last observation carried forward
[b]Mean change from baseline
[c]p-value is based on analysis of covariance with treatment as factor and baseline as covariate

The 0.3 mg CE/1.5 mg MPA dosage shows a statistically significant reduction in MSVS (frequency and severity) when compared to placebo at Week 4 and Week 12. There is a decrease of greater than 2 moderate-to-severe hot flushes per day in the 0.3 mg CE/ 1.5 mg MPA group compared to the placebo that is evident at Week 4 and maintained through Week 12. In addition, the Sponsor also performed subgroup analysis of VMS by age in those subjects who completed 12 weeks of treatment. The results by age group (<50, 50-59, ≥ 60) showed that in women < 50, the 0.3 mg CE/1.5 mg MPA dosage strength demonstrated a delay in treatment effect for reduction in the number of MSVS (not evident until Week 8) and no treatment effect for severity at Weeks 4, 8, or 12. In women age 50-59, the 0.3 mg CE/1.5 mg MPA was statistically significantly better than placebo in reducing the number and severity of VMS at Weeks 4, 8, and 12. The ≥ 60 age group had too few women to permit an assessment of treatment effect.

The efficacy in treatment of VVA was assessed utilizing baseline, on-treatment and end-of-study vaginal cytology smears to determine the maturation Index (MI= the percentage of parabasal, intermediate and superficial cells). The Division now strongly recommends that studies for efficacy in the treatment of VVA assess physician-determined signs and patient's symptoms in addition to the MI. However, this recommendation was not being made when the original protocol for the HOPE study was reviewed. MI data is presented in Table 3 that was modified from the MO's Table 4.

Table 3. Maturation Index per Treatment Group assessed between Cycles 5-7 and Cycles 12-14, ITT Population

Treatment	Baseline Mean ±SE	Cycle 5-7 Mean Change± SE	Cycle 12-14 Mean Change ±SE
0.3 mg CE/ 1.5 mg MPA			
Parabasal Cells (%)	33.3 ± 2.3	-26.6 ± 2.2	-27.9 ± 2.5
Intermediate Cells (%)	59.6 ± 2.0	17.2 ± 2.0	18.2 ± 2.1
Superficial Cells (%)	7.1 ± 0.7	9.4 ± 1.1	9.7 ± 1.0
p-value vs. placebo		<0.001	<0.001
Placebo			
Parabasal Cells (%)	36.5 ± 2.3	2.4 ± 2.2	2.3 ± 2.2
Intermediate Cells (%)	56.8 ± 2.1	-3.2 ± 2.0	-3.1 ± 2.1
Superficial Cells (%)	6.8 ± 0.6	0.8 ± 1.0	0.7 ± 1.0

Table 3 demonstrates that an estrogenic effect is shown for both the cycle 6 and cycle 13 evaluations for the 0.3 mg CE/1.5 mg MPA dosage strength.

The efficacy in protection of the endometrium was evaluated based on the rate of endometrial hyperplasia and endometrial cancer as assessed by endometrial biopsy at baseline, between cycles 5-7 and between cycles 12-14. Endometrial hyperplasia is evaluated in clinical trials as a surrogate for endometrial carcinoma, because it is rare to see more than 1 to 2 endometrial cancers in most large clinical trials. Evaluable subjects were those who had taken at least one dose of study medication and had both a prestudy endometrial biopsy and an in-study endometrial biopsy performed during cycles 5 to 7 and cycles 12 to 14 or who developed endometrial hyperplasia at any time during the first year of the study. The study protocol followed the proposed revisions to 1995 HRT Guidance with respect to diagnosis of hyperplasia. Two thousand one hundred fifty three (2,153) subjects were included in the primary analysis of endometrial hyperplasia and cancer by cycle 13. The Sponsor's analysis showed no endometrial cancer occurring during the course of the study. However, the clinical review led to a reclassification of two cases of hyperplasia (per the Sponsor) to endometrial carcinoma (per the clinical reviewers). The cycle 5-7 endometrial biopsy of subject 30924-0011 (0.3 mg CE) was read as complex hyperplasia with atypia by study pathologist 1 and endometrial adenocarcinoma, focal by study pathologist 2. The third adjudicating study pathologist, as specified in the protocol, did not read the slides. The patient withdrew from the study and had her slides re-read by an unblinded gynecologic oncologist, who agreed with the diagnosis of study pathologist 2. The Sponsor assigned this case as hyperplasia. However, because the third assessor was outside of the study and was not blinded, this diagnosis should not be considered. Taking into consideration the most conservative diagnosis ("worst case") between pathologist 1 and pathologist 2, the clinical reviewing team reclassified this diagnosis as endometrial adenocarcinoma. The cycle 5-7 endometrial biopsy of subject 30912-0049 (0.45 mg CE/ 1.5 mg MPA) was read as complex hyperplasia with atypia in a polyp by pathologist 1, endometrial adenocarcinoma involving an endometrial polyp by pathologist 2, and endometrial adenocarcinoma in a polyp by pathologist 3. The Sponsor assigned this case as hyperplasia. The clinical review team reclassified this case as endometrial adenocarcinoma following the HRT Guidance document recommendation that the majority diagnosis, two of the three pathologists, is the accepted final diagnosis. A third case was also reviewed for difficulty in the diagnosis. The cycle 5-7 endometrial biopsy of subject 30908-0003 (0.3 mg CE/1.5 mg MPA) was read as back-to-back glandular architecture, can not rule out hyperplasia by pathologist 1, complex hyperplasia with atypia by pathologist 2 and atypical glandular proliferation by pathologist 3. All three pathologists disagreed as to diagnostic severity. The Sponsor assigned this subject as

hyperplasia. Following the HRT Guidance document scheme, since all three pathologists essentially disagreed, the clinical review team considered the worst case scenario and assigned this subject a diagnosis of complex hyperplasia with atypia. The rate of endometrial hyperplasia for all treatment groups is shown below in Table 4, modified from MO Table 5.

Table 4 Incidence of Endometrial Hyperplasia at Cycle 13,

Treatment	n	Total number of Hyperlasias	Hyperplasia rate (one-sided 95% CI)	p-value vs. CE alone
0.625 mg CE	249	20	8.03 (0, 11.5)	N/A.
0.625 mg CE/2.5 mg MPA	278	0	0.00 (0, 1.1)	<0.001
0.45 mg CE	279	9	3.23 (0, 5.6)	N/A
0.45 mg CE/2.5 mg MPA	273	0	0.00 (0, 1.1)	0.004
0.45 mg CE/1.5 mg MPA	272	0	0.00 (0, 1.2)	0.004
0.3 mg CE	269	0	0.00 (0, 1.1)	N/A
0.3 mg CE/ 1.5 mg MPA	272	1	0.37 (0, 1.8)	1.00
Placebo	261	0	0.00 (0,1.2)	

Typically 0 to 1 cases of endometrial carcinoma are seen in combination estrogen/progestin products in controlled clinical trials. This trial was not unusual in that one case of endometrial adenocarcinoma was seen in the 0.45 mg CE/1.5 mg MPA combination dosage strength. The rate of hyperplasia for this dosage strength (as well as all other CE/MPA combinations studied) clearly is acceptable when judged according to the revised HRT Guidance that states that the rate of hyperplasia for a combination estrogen/progestational drug product should be ≤ 1% and the upper limit of a one-sided 95 % confidence interval for the risk of endometrial hyperplasia should not exceed 4%.

The rate of cumulative amenorrhea (percentage of subjects per treatment group who become amenorrheic and remain so throughout the study year) is presented in the label of combination estrogen/progestin products. The cumulative rate of amenorrhea was acceptable for the 0.30 mg CE/ 1.5 mg MPA dosage strength and at cycle 13 was comparable to that of placebo.

Two deaths were reported during Study 0713D2-309-US. Both of these were lung cancer deaths and were considered unrelated to study drug medication. Eight breast cancers were reported in the interim analysis at 1 year of Study 0713D2-309. Seven of these cancers occurred during treatment and 1 case was diagnosed 1 year after treatment and is reported in the interim analysis. Four of the breast cancers were in the 0.3 mg CE/1.5 mg MPA treatment group and 1 case of breast cancer was reported in each of the 0.625 mg CE, the 0.625mg CE/1.5 mg MPA, the 0.45 mg CE/1.5 mg MPA and placebo treatment groups. No cases of breast cancer were seen in the 0.45 mg CE, the 0.45mg CE/2.5 mg MPA or the 0.3 mg CE treatment groups at 1-year. In addition to the 8 cases of breast cancer in study year 1, one subject (Subject 30919-0066 assigned to placebo) was shown to have a pre-cancerous lobular carcinoma in situ (multiple foci, with calcifications, cystic change, and apocrine metaplasia) upon mammotome biopsy of a suspicious mammographic lesion at cycle 13.

In year 2 of the osteoporosis substudy, 3 additional subjects were reported to have breast cancer at cycle 26/27, and 1 subject had breast cancer reported post-study. One case of breast cancer was reported in each of the following treatment groups: 0.45 mg CE alone, 0.45 mg CE/1.5 mg MPA, 0.3 mg CE alone (reported approximately 9 months post-study), and placebo. In total, 12 cases of breast cancer were reported during the conduct of the 2-year HOPE study (7 in year 1, 3 in year 2, and 2 post-study). Three cases of breast cancer occurred in CE alone treatment groups (one in each CE alone treatment group), seven cases of breast cancer occurred in combination

CE/MPA treatment groups (only the 0.45 mg CE/2.5 mg MPA dosage strength was free of reported breast cancer), and 2 cases occurred in the placebo treatment group. While 4 cases of breast cancer were reported with the 0.3 mg CE/1.5 mg MPA dosage strength in year 1 of the HOPE study, no additional cases were reported for this dosage strength in year 2.

Overall, 12 cases of breast cancer in 2,673 treated subjects do not represent a higher incidence of breast cancer than reported for other large HRT clinical trials conducted over a two-year period. However, the results of the HOPE study underscore the need for Clinicians to be vigilant and to perform the appropriate surveillance procedures to identify lesions of the breast in their patients on combination estrogen/progestin or estrogen-alone replacement therapy. The recently published results of the Women's Health Initiative demonstrating an increased risk for Breast Cancer for women receiving Prempro 0.625 mg CE/2.5 mg MPA compared to placebo further emphasize the need for appropriate counseling and surveillance of women taking estrogen/progestin hormone replacement therapy.

Other serious adverse events reported in year 1 of the HOPE study include 4 cases of arterial thrombosis, and three venous thromboembolic events. No additional cases of arterial or venous thrombosis were reported in year 2 of the HOPE study. The numbers of these two events in a total of 2,673 subjects did not appear to the clinical reviewers to be excessive or out of line with previous trials of combination estrogen /progestin products. A total of 266 subjects (10%) discontinued the study due to adverse events. Among the subjects treated in the combination estrogen/progestin groups, the rate of discontinuation was 9%. The rate of discontinuations due to adverse events is not unusual for this size study and does not raise concern for safety. Women treated with CE alone (0.625 mg, 0.45 mg and 0.3 mg) in general had a more favorable increase in HDL-C and HDL_2-C concentrations than women treated with CE/MPA (0.625 mg CE/2.5 mg MPA, 0.45 mg CE/2.5 mg MPA, 0.45 mg CE/1.5 MPA and 0.3 mg CE/1.5 mg MPA). This is expected.

Division of Scientific Investigations (DSI) Report

Following the DSI guidelines regarding criteria for requesting inspection of clinical sites, the medical officer determined that this efficacy supplement had no specific safety concerns and did not require inspection.

Clinical Pharmacology and Biopharmaceutics

Two bioavailability studies were provided to support the clinical pharmacology and biopharmaceutics of S-017. These were referenced for S-024. The studies were both randomized, single dose, 4 period/treatment crossover studies. In Study 0713D2-119-US, the following estrogen/progestin combination or estrogen-alone doses were evaluated: 2 x 0.625 mg CE/2.5 mg MPA, 2 x 0.45 mg CE/ 2.5 mg MPA, 2 x 0.45 mg CE/1.5 mg MPA, and 2 x 0.45 mg CE. Study 0713 D2-120 evaluated 2 x 0.625 mg CE/2.5 mg MPA, 2 x 0.45 mg CE/1.5 mg MPA, 2 x 0.3 mg CE/1.5 mg MPA and 2 x 0.3 mg CE alone. The results of the two bioavailability studies demonstrate that CE and MPA behaved pharmacokinetically in a dose-related manner, and MPA had no effect on the pharmacokinetics of CE. The biopharmaceutics reviewer concluded that the formulations (CE/MPA and CE) tested in the above bioavailability studies, are identical to the to-be-marketed formulations in terms of scale of manufacture and composition except in the color coat, which was white in the clinical formulation. The color change between the clinical batch and the to-be-marketed batch was justified by *in vitro* dissolution data.

The Sponsor's proposed in vitro dissolution method is acceptable. However, the recommended in vitro dissolution specifications are: at 2 hours (b) (4) released, at 5 hours (b) (4) released, at 8 hours NLT(b) (4)

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB DPEII) finds the information submitted in the NDA to be acceptable.

Preclinical Pharmacology and Toxicology

The Pharmacology Team has no concerns related to the Pharmacology and Toxicology of the 0.30 mg CE/1.5 mg MPA dosage strength. The Pharmacology team recommends approval of S-024.

Chemistry, Manufacturing and Controls (CMC)

The drug substances are identical to those in the approved dosage strength tablets and the drug product manufacturing process is identical to the approved process. The CMC information on the drug substance and drug product was found to be satisfactory (see CMC review). The Office of Compliance issued an overall Withhold recommendation based on an unsatisfactory cGMP inspection at the Wyeth Laboratories facility in Rouses Point, NY. From a CMC perspective, the application is Approvable. Before the application may be approved, it will be necessary for the Wyeth Laboratories facility in Rouses Point, NY to have a satisfactory cGMP inspection and all CMC facilities listed in the application must be in cGMP compliance.

Conclusions and Recommendations

The safety and efficacy data presented in S-024 support the approval of the 0.30 mg CE/1.5 mg MPA dosage strength for the treatment of VMS and VVA in women with a uterus. The claim of protection of the endometrium is adequately supported. I concur with the recommendation of the primary clinical reviewer that the 0.30 mg/1.5 mg MPA dosage strength can be approved. However, before the application may be approved, it will be necessary for the Wyeth Laboratories facility in Rouses Point, NY to have a satisfactory cGMP inspection. The Sponsor must also agree to the labeling changes in the Approvable letter.

Shelley R. Slaughter, MD, Ph.D.
Reproductive Medical Officer Team Leader

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

/s/

Shelley Slaughter
8/28/02 02:05:13 PM
MEDICAL OFFICER

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-527/S-024, S-026, S-031

CHEMISTRY REVIEW(S)

CHEMIST REVIEW #1
OF **SUPPLEMENT**

1. **ORGANIZATION:** DRUDP HFD-580
2. **NDA NUMBER:** 20-527/SE1-024
3. **SUPPLEMENT NUMBERS/DATES:**
   Letterdate: 05-NOV-2001
   Stampdate: 07-NOV-2001
4. **AMENDMENTS/REPORTS/DATES:**
   Letterdate: 25-JAN-2002
   Stampdate: 28-JAN-2002
5. **RECEIVED BY CHEMIST:** 11-NOV-2001

6. **APPLICANT NAME AND ADDRESS:**
   Wyeth-Ayerst Laboratories
   P.O. Box 8299
   Philadelphia, PA 19101-8299

7. **NAME OF DRUG:**
   Prempro/Premphase Tablets

8. **NONPROPRIETARY NAME:**
   Conjugated estrogens, USP/medroxyprogesterone acetate, USP

9. **CHEMICAL NAME/STRUCTURE:**
   a. Conjugated estrogens (CE): see USP 24

   b. Medroxyprogesterone acetate (MPA): Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, (6α)-
   See USP for structural formula

10. **DOSAGE FORM(S):**
    Tablets

11. **POTENCY:**
    0.625 mg CE/2.5 or 5 mg MPA (approved), *0.3 mg CE/1.5 mg MPA*

12. **PHARMACOLOGICAL CATEGORY:**
    Estrogen, progestin/Hormone replacement therapy

13. **HOW DISPENSED:**
    RX

14. **RECORDS & REPORTS CURRENT:**
    Yes

15. **RELATED IND/NDA/DMF:**

    NDA 4-782

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				3	Adequate	2/22/01	Reviewed by Dr. D. Lin

(b) (4)	1	Adequate	5/21/02	Reviewed by Dr. D. Lin
	3	Adequate	3/31/01	Reviewed by Dr. D. Lin
	3	Adequate	7/29/99	Reviewed by Dr. D. Lin
	3	Adequate	4/23/98	Reviewed by Dr. A. Al-Hakim
	3	Adequate	9/27/00	Reviewed by Dr. R. Lostritto
	3	Adequate	3/27/01	Reviewed by Dr. D. Lin
	7	N/A	N/A	The relevant information in this DMF have been transferred to DMF (b) (4)
	7	N/A	N/A	The relevant information in this DMF have been transferred to DMF (b) (4)
	3	Adequate	3/25/01	Reviewed by Dr. D. Lin
	3	Adequate	3/26/01	Reviewed by Dr. D. Lin
	3	Adequate	2/9/01	Reviewed by Dr. D. Klein
	3	Adequate	9/28/00	Reviewed by Dr. D. Klein
	3	Adequate	3/24/00	Reviewed by Dr. D. Klein
	3	Adequate	3/31/01	Reviewed by Dr. D. Lin
	3	Adequate	3/2/00	Reviewed by Dr. D. Christodoulou
	3	Adequate	12/4/00	Reviewed by Dr. M. Adams
	3	Adequate	8/11/00	Reviewed by

		Medical (b) (4)	coil	3	Adequate	4/20/00	Dr. R. Trimmer Reviewed by Dr. S. Markosky

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

16. SUPPLEMENT PROVIDES FOR:
A new lower dosage strength drug product tablets, 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate.

17. COMMENTS
This efficacy supplement provides for a lower dosage strength tablets of conjugated estrogens (CE) and medroxyprogesterone acetate (MPA) [0.3 mg CE/1.5 mg MPA] in a continuous regimen for the treatment of moderate to severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy. The drug substances are identical to those in the approved dosage strength tablets and the drug product manufacturing process is identical to the approved process.

The 0.3 mg/1.5 mg dosage strength tablet, along with the 0.45 mg/1.5 mg strength tab let, was originally submitted to Supplement S-017 for approval but the 0.3 mg/1.5 mg strength was withdrawn from that supplement (see 4/3/01 amendment). Although this supplement covers the 0.3 mg CE/1.5 mg MPA strength tablet from a clinical point of view, CMC information for both the 0.3 mg CE/1.5 mg MPA and 0.45 mg CE/1.5 mg MPA strength tablets have been provided. Therefore, this review is a repeat of the review for supplement S-017, except for updates in the following sections: 1) MPA drug substance DMF update; 2) drug product stability update; and 3) updated cGMP inspection.

The February 25, 2002 general correspondence contains a cross-reference to NDA 20-527 Supplement S-017 for CMC information and a description of the differences between what is submitted to that supplement and to this NDA.

18. CONCLUSIONS AND RECOMMENDATIONS:
From a Chemistry, Manufacturing and Controls point of view, this Efficacy Supplement may be approved pending satisfactory resolution of the deficiency below. **Issue an Approvable recommendation with the following statement. Before this application may be approved, it will be necessary to address the following:**

- **The Wyeth Laboratories facility in Rouses Point, NY must have a satisfactory cGMP inspection. In addition, all facilities listed in this application must be in cGMP compliance.**

19. REVIEWER NAME **SIGNATURE** **DATE COMPLETED**
David T. Lin, Ph.D. 26-JUN-2002
Chemistry Team Leader

cc: Original: NDA 20-527/SE1-024
HFD-580/Division File
HFD-580/DSpellLesane
HFD-580/DLin

INIT

Filename: S20527.024 (doc)

36 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

David T. Lin
8/21/02 05:30:05 PM
CHEMIST

CHEMIST REVIEW #2
OF **SUPPLEMENT**

1. **ORGANIZATION:** DRUDP HFD-580
2. **NDA NUMBER:** 20-527/SE1-024
3. **SUPPLEMENT NUMBERS/DATES:**
   Letterdate: 05-NOV-2001
   Stampdate: 07-NOV-2001
4. **AMENDMENTS/REPORTS/DATES:**
   Letterdate: See list on page 5
   Stampdate: See list on page 5
5. **RECEIVED BY CHEMIST:** 18-MAR-2003

6. **APPLICANT NAME AND ADDRESS:**
   Wyeth-Ayerst Laboratories
   P.O. Box 8299
   Philadelphia, PA 19101-8299
   (484)-865-3749

7. **NAME OF DRUG:**
   Prempro™/Premphase® Tablets

8. **NONPROPRIETARY NAME:**
   Conjugated estrogens/medroxyprogesterone acetate

9. **CHEMICAL NAME/STRUCTURE:**
   Conjugated estrogens (CE) – Please refer to USP 26.
   Medroxyprogesterone acetate (MPA) – Preg-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, 6α
   (Please refer to USP 26 for structural formula.)

10. **DOSAGE FORM(S):**
    Tablets

11. **POTENCY:**
    0.45 mg CE/1.5 MPA, 0.625 mg CE/2.5 mg MPA or 0.625 mg CE/5 mg MPA (approved)
    0.3 mg CE/1.5 mg MPA

12. **PHARMACOLOGICAL CATEGORY:**
    Estrogen/progestin, Hormone replacement therapy

13. **HOW DISPENSED:**
    Rx

14. **RECORDS & REPORTS CURRENT:**
    Yes

15. **RELATED IND/NDA/DMF:**
    None

16. **SUPPLEMENT PROVIDES FOR:**
    A new lower dosage strength drug product tablet, 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate.

17. **SPECIAL PRODUCTS: YES _X_ NO ___** (A form for this NDA has already been submitted).

18. **COMMENTS**

This efficacy supplement provides for a lower dosage strength tablet of conjugated estrogens (CE) and medroxyprogesterone acetate (MPA) [0.3 mg CE/1.5 mg MPA] in a continuous regimen for the treatment of moderate to severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy. The drug substances are identical to those in the approved dosage strength tablets, and the drug product manufacturing process is identical to the approved process.

This review covers materials submitted by the Sponsor (please refer to the list on page 4) as a complete response to the approvable letter issued by the Agency on 28-AUG-2002 for NDA 20-527/SE1-024.

NDA 20-527/SE1-024 was deemed approvable from a CMC standpoint, based on GMP compliance issues. These items are discussed in the applicable sections of the attached review.

Based on data presented in the 28-FEB-03 and 5-MAR-03 amendments to NDA 20-527/SE2-017, an interim in-process, release, and stability dissolution acceptance criterion for CE at the five hour timepoint has been established. The in-process acceptance criterion is (b) (4) and the release and stability acceptance criterion is (b) (4) .

In the 2-APR-2003 amendment to NDA 20-527/SE1-024, the Sponsor confirmed that the previously-developed acceptance criteria would be applied to the 0.3 mg/1.5 mg (CE/MPA) dosage strength.

The following are agreements that have been made with the Sponsor and need to be included in the Action Letter:

1. The Agency has agreed to an interim release and stability specification for CE dissolution at the 5 hour timepoint. This interim acceptance criterion is (b) (4) .
2. The Sponsor has committed to Dissolution Surveillance Program for the dissolution of conjugated estrogens in the 0.3 mg/1.5 mg Premarin/MPA drug product. In this commitment, every packaged lot will be tested for CE dissolution at six-month intervals. This surveillance program will be performed through expiration of the product.

19. **CONCLUSIONS AND RECOMMENDATIONS:**

From a CMC standpoint, this supplement is acceptable and may be approved.

20. **REVIEWER NAME**	**SIGNATURE**	**DATE COMPLETED**
Sarah Pope		30-APR-2003

cc: Original: NDA 20-527/SE1-024
HFD-580/Division File

HFD-580/KSherrod
HFD-580/DLin/SPope

Filename: Prempro/20527_S024.doc

5 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Establishment Evaluation Report (EER)

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 20527/024	Action Goal:	
Stamp:	07-NOV-2001	District Goal:	03-AUG-2002
Regulatory Due:	14-MAY-2003	Brand Name:	PREMPRO/PREMPHASE
Applicant:	WYETH PHARMACEUTICALS INC	Estab. Name:	
	8299	Generic Name:	CONJUGATED
	PHILADELPHIA, PA 191018299		ESTROGENS/MEDROXYPROGEST
Priority:	3S		ERONE
Org Code:	580	Dosage Form:	(EXTENDED-RELEASE TABLET
		Strength:	SEE COMMENTS

Application Comment: THE CURRENT APPROVED DOSAGE STRENGTH IS 0.625 MG CONJUGATED ESTROGENS/2.5 MG OR 5 MG MEDROXYPROGESTERONE ACETATE. THIS SUPPLEMENT IS FOR ONE NEW DOSAGE STRENGTH TABLET: 0.3 MG CONJUGATED ESTROGENS/1.5 MG MEDROXYPROGESTERONE ACETATE. (on 28-DEC-2001 by D. LIN (HFD-580) 301-827-4230)
THESE SITES ARE BEING RESUBMITTED. THE SPONSOR HAS SUBMITTED A RESPONSE TO THE APPROVABLE LETTER (AUGUST 28, 2002), STATING THAT THE DEFICIENCIES IN THE GUAYAMA, PUERTO RICO AND ROUSES POINT SITES HAVE BEEN CORRECTED. THEREFORE, CURRENT CONFIRMATION IS NEEDED, THAT ALL SITES LISTED IN N20527, SE1-024 ARE IN COMPLIANCE. (on 24-MAR-2003 by S. POPE (HFD-580) 301-827-4260)

FDA Contacts:	D. MOORE	(HFD-180)	301-827-7476	, Project Manager
	D. LIN	(HFD-580)	301-827-4230	, Review Chemist

Overall Recommendation: ACCEPTABLE on 02-MAY-2003by R. WOODS (HFD-322)301-827-9011
WITHHOLD on 30-MAY-2002by P. LEFLER(HFC-130)301-827-5636

Establishment: CFN 9613692 FEI 3002806438
AYERST ORGANICS INC
R7A 7H2
BRANDON, MANITOBA, CA

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CEX OAI Status: NONE

Estab. Comment: CONJUGATED ESTROGENS DRUG SUBSTANCE MANUFACTURER. (on 28-DEC-2001 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-DEC-2001				LINDAV
OC RECOMMENDATION	31-DEC-2001			ACCEPTABLE BASED ON PROFILE	GARCIAM
SUBMITTED TO OC	24-MAR-2003				POPES
OC RECOMMENDATION	24-MAR-2003			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: CFN 2650135 FEI 3003108339

05-MAY-2003 FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

AYERST WYETH PHARMACEUTICALS

STATE ROAD 3 KM 142.1

GUAYAMA, PR 00784

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TTR OAI Status: NONE

Estab. Comment: DRUG PRODUCT MANUFACTURER. (on 28-DEC-2001 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-DEC-2001				LINDAV
SUBMITTED TO DO	31-DEC-2001	10D			DAMBROGIOJ
ASSIGNED INSPECTION T	31-DEC-2001	PS			MTORRES
INSPECTION SCHEDULED	13-FEB-2002		18-MAR-2002		MTORRES
INSPECTION PERFORMED	09-APR-2002		19-MAR-2002		MTORRES
DO RECOMMENDATION	09-APR-2002			ACCEPTABLE INSPECTION	MTORRES

COMPREHENSIVE GMP COVERAGE FOUND FIRM NAI. APPLICATION COVERED 9/99. VALIDATION PENDING RESOLUTION OF ISSUES RELATED TO DISSOLUTION IN PREMARIN PRODUCT; FACTORS IDENTIFIED AT SITE AND CORRECTIVE ACTIONS HAVE BEEN IMPLEMENTED. NO DEVIATIONS ASSOCIATED WITH THIS OR OTHER RELATED PRODUCTS IDENTIFIED. PRODUCT IS CO-MAUFACTURED AT ROUSES POINT.

OC RECOMMENDATION	09-APR-2002			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ
SUBMITTED TO OC	24-MAR-2003				POPES
SUBMITTED TO DO	24-MAR-2003	10D			DAMBROGIOJ
DO RECOMMENDATION	08-APR-2003			ACCEPTABLE BASED ON FILE REVIEW	MSOSA
OC RECOMMENDATION	08-APR-2003			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

(b) (4)

DMF No: (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

Estab. Comment: MEDROXYPROGESTERONE ACETATE DRUG SUBSTANCE MANUFACTURER. (on (b) (4)
(b) (4) by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-DEC-2001				LINDAV
OC RECOMMENDATION	31-DEC-2001			ACCEPTABLE BASED ON PROFILE	GARCIAM

05-MAY-2003

FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

SUBMITTED TO OC	24-MAR-2003		POPES
OC RECOMMENDATION	24-MAR-2003	ACCEPTABLE	DAMBROGIOJ
		BASED ON PROFILE	

Establishment: CFN (b) (4) FEI (b) (4)

(b) (4)

DMF No: (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: (b) (4) OAI Status: NONE

Estab. Comment: MEDROXYPROGESTERONE ACETATE DRUG SUBSTANCE MANUFACTURER. (on (b) (4) (b) by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-DEC-2001				LINDAV
OC RECOMMENDATION	31-DEC-2001			ACCEPTABLE	GARCIAM
				BASED ON PROFILE	
SUBMITTED TO OC	24-MAR-2003				POPES
OC RECOMMENDATION	24-MAR-2003			ACCEPTABLE	DAMBROGIOJ
				BASED ON PROFILE	

Establishment: CFN (b) (4) FEI (b) (4)

(b) (4)

DMF No: (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE MICRONIZER

Profile: (b) (4) OAI Status: NONE

Estab. Comment: MEDROXYPROGESTERONE ACETATE DRUG SUBSTANCE (b) (4) (on (b) (4)
by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-DEC-2001				LINDAV
SUBMITTED TO DO	31-DEC-2001	GMP			GARCIAM
DO RECOMMENDATION	31-DEC-2001			ACCEPTABLE BASED ON FILE REVIEW	GARCIAM
4/14/00					
OC RECOMMENDATION	31-DEC-2001			ACCEPTABLE DISTRICT RECOMMENDATION	GARCIAM

FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

SUBMITTED TO OC	24-MAR-2003		POPES
OC RECOMMENDATION	24-MAR-2003	ACCEPTABLE	DAMBROGIOJ
		BASED ON FILE REVIEW	

AC 4/14/00

Establishment: CFN 1310337 FEI 1310337

WYETH LABORATORIES INC

64 MAPLE ST

ROUSES POINT, NY 12979

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE OTHER TESTER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

Profile: CEX OAI Status: NONE

Estab. Comment: CONJUGATED ESTROGENS DRUG SUBSTANCE MANUFACTURER. (on 28-DEC-2001 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-DEC-2001				LINDAV
OC RECOMMENDATION	31-DEC-2001			ACCEPTABLE	DAMBROGIOJ
				BASED ON PROFILE	
SUBMITTED TO OC	24-MAR-2003				POPES
SUBMITTED TO DO	24-MAR-2003	10D			DAMBROGIOJ
DO RECOMMENDATION	03-APR-2003			ACCEPTABLE	JPODSADO
				BASED ON FILE REVIEW	
LAST INSPECTION (11/13-15/2002) FOUND CEX AS ACCEPTABLE.					
OC RECOMMENDATION	04-APR-2003			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	

Profile: TTR OAI Status: POTENTIAL OAI

Estab. Comment: DRUG PRODUCT MANUFACTURER. (on 28-DEC-2001 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-DEC-2001				LINDAV
SUBMITTED TO DO	31-DEC-2001	10D			DAMBROGIOJ
DO RECOMMENDATION	11-JAN-2002			WITHHOLD PREVIOUS DEVIATIONS PERSIST	JPODSADO

THE LAST GMP INSPECTION (2/1/2001) IN FACTS CLASSIFIES THE PROFILE CLASS "TTR" AS UNACCEPTABLE.

OC RECOMMENDATION	30-MAY-2002			WITHHOLD DISTRICT RECOMMENDATION	ALCOCKP

DUE TO CONTINUED CGMP CONCERNS WITH PREMARIN AND PREMPRO FIRM IS NOT ACCEPTABLE FOR

05-MAY-2003

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

CGMPS FOR THESE TWO PRODUCTS. REFER TO PREVIOUS DO AND OC RECOMMENDATIONS AND SUPPORTING INFO FOR REASON FOR WITHHOLD. UNTIL RESOLUTION OCCURS FOR PREMARIN/PREMPRO - FIRM IS UNACCEPTABLE

SUBMITTED TO OC	24-MAR-2003		POPES
SUBMITTED TO DO	24-MAR-2003 10D		DAMBROGIOJ
DO RECOMMENDATION	04-APR-2003	WITHHOLD	JPODSADO

PREVIOUS DEVIATIONS PERSIST

ALTHOUGH THE PROFILE TTR IS CONSIDERED ACCEPTABLE FOR THIS FIRM, ALL TTR PREMARIN TABLETS AND TTR PREMARIN (b) (4) ARE CONSIDERED UNACCEPTABLE. SOME LOTS OF TTR PREMARIN TABLETS (OR (b) (4)) CONTINUE TO FAIL FINISHED PRODUCT RELEASE OR STABILITY DISSOLUTION SECIFICATIONS. THE FIRM CONTINUES TO RECALL TTR PREMARIN DRUG PRODUCTS DUE TO DISSOLUTION FAILURES. AN ADDITIONAL FIVE LOTS WERE INCLUDED UNDER THE FIRM'S ONGOING RECALLS ON 3/31/2003.

OC RECOMMENDATION	02-MAY-2003	ACCEPTABLE	WOODSR

FIRM RESPONSE TO DEFIC. ADEQUA

THIS ACCEPTABLE RECOMMENDATION PERTAINS ONLY TO LOW DOSE STRENGTHS OF WYETH'S PREMPRO (CONJUGATED ESTROGENS/MEDROXYPROGESTERONE ACETATE TABLETS), SUBJECT OF THIS SUPPLEMENT. NOTE THAT EES SHOWS A 4/4/03 DISTRICT OFFICE (DO) RECOMMENDATION OF WITHHOLD FOR THE GMP STATUS OF THIS APPLICATION EVEN THOUGH THE FACTS PROFILE CLASS FOR THIS PRODUCT HAS A DO RECOMMENDATION OF ACCEPTABLE. THE REMARKS SECTION OF THE DO WITHHOLD RECOMMENDATION NOTES AN EXCEPTION TO THE ACCEPTABLE PROFILE CLASS, EXPLAINING THAT WYETH'S ROUSES POINT, NY FACILITY (CFN 1310337) IS UNACCEPTABLE FOR MANUFACTURING PREMARIN (CONJUGATED ESTROGEN) TABLETS DUE TO SPECIFIC GMP PROBLEMS IDENTIFIED WITH THIS DRUG PRODUCT.

HOWEVER, CDER/OC HAS EVALUATED THE OUTSTANDING CGMP ISSUES AND CURRENT DISTRICT OFFICE WITHHOLD RECOMMENDATION IN CONJUNCTION WITH THE FOLLOWING INFORMATION PROVIDED THROUGH HFD-300:

IN LIGHT OF RECENT FINDINGS FROM THE WHI STUDY AND KNOWN DOSE-RESPONSE DATA FOR ESTROGEN-CONTAINING PRODUCTS, LOWER STRENGTHS OF PREMPRO HAVE THEORETICAL PUBLIC HEALTH BENEFITS OVER HIGHER STRENGTHS. ADDITIONALLY, RECENT PRODUCT FAILURES ONLY INVOLVE HIGHER

FAILURES OR OTHER SIGNIFICANT PROBLEMS.

BASED ON OUR EVALUATION OF THE ABOVE INFO AND DIRECTIONS FROM HFD-300 EES HAS BEEN UPDATED TO REFLECT AN ACCEPTABLE GMP STATUS FOR THIS SUPPLEMENT. AGAIN, THIS ACCEPTABLE RECOMMENDATION ONLY APPLIES TO LOW DOSE STRENGTHS OF THIS SUPPLEMENT. (I.E. LESS THAN .625 MG)

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

/s/

Sarah Pope
5/7/03 01:50:43 PM
CHEMIST

David T. Lin
5/7/03 04:05:54 PM
CHEMIST
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-527/S-024, S-026, S-031

ENVIRONMENTAL ASSESSMENT

July 30, 2001

Environmental Assessment

Statement of Compliance

Wyeth-Ayerst Pharmaceuticals states that an Environmental Assessment (EA) for the proposed action, a supplement to the New Drug Application (NDA No. 20-527) for the use of Prempro™ (conjugated estrogens/medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg) for the treatment of vasomotor symptoms associated with menopause and treatment of vulvar and vaginal atrophy, is categorically excluded according to 21 CFR 25.31(b).

The aforementioned regulation states that a categorical exclusion is permitted for "Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion." The Expected Introduction Concentration (EIC) of conjugated estrogens is below one part per billion. The EIC of medroxyprogesterone acetate is also below one part per billion.

To the best knowledge of Wyeth-Ayerst Pharmaceuticals, no extraordinary circumstances exist associated with the proposed action.

Craig F. Seyfried
Senior Director
Environmental Health & Safety
Wyeth-Ayerst Pharmaceuticals

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

PREMPRO™ AND PREMPHASE™

(conjugated estrogens / medroxyprogesterone acetate)

TABLETS

NDA 20-527

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS (HFD-510)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-527

PREMPRO™ AND PREMPHASE™

(conjugated estrogens / medroxyprogesterone acetate)

TABLETS

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for PREMPRO™ and PREMPHASE™, Wyeth-Ayerst Laboratories has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Conjugated estrogens, one of the two active ingredients, is a natural product. It contains a mixture of estrogens obtained exclusively from natural sources, occurring as the sodium salts of water soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares urine. Medroxyprogesterone acetate, the other of the two active ingredients, is (b) (4) The two active ingredients are orally administered concomitantly as a combined tablet in the treatment of, in women with an intact uterus, (1) moderate to severe vasomotor symptoms associated with the menopause, (2) vulval and vaginal atrophy, and (3) prevention of osteoporosis. The drug will be manufactured by (b) (4)

Wyeth-Ayerst Laboratories, 64 Maple Street Rouses Point, New York 12979 (conjugated estrogens drug substance; drug product), (b) (4)

(medroxyprogesterone acetate drug substance). The finished drug product will be used in hospitals, clinics, and/or by patients in their homes, the latter being the most likely.

As a result of patient use, the active ingredients and/or their metabolites, the latter being the most likely, will enter the environment by excretion into the public wastewater and sewage treatment facilities. Manufacturing wastes containing the drug substances and/or their degradation products will be discharged, after treatment at the manufacturing site, into the public wastewater and sewage treatment facilities, or, transferred to landfills. Chemical and physical tests indicate that the drug substances, their metabolites and/or degradation products will most likely be restricted to the aquatic environment and will be biodegraded.

Studies described in the Environmental Assessment show that the two active ingredients are rapidly degraded and therefore are not expected to persist in the environment. No toxicity of the drug substances to atmospheric, aquatic, or terrestrial organisms is expected. Toxicological studies performed on microbial organisms, mice and rats show that the drug substances are relatively non-toxic.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at licensed incineration facilities or landfills. At U.S. hospitals and clinics, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

Nov. 13, 1995
DATE

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Attachments: Environmental Assessment
Material Safety Data Sheets (MSDSs) for conjugated estrogens and medroxyprogesterone acetate (drug substances)

ENVIRONMENTAL ASSESSMENT INFORMATION

CONJUGATED ESTROGENS/MPA COMBINATION TABLET

November 6, 1995

TABLE OF CONTENTS

		Page
1.	DATE	4
2.	NAME OF APPLICANT	4
3.	ADDRESS	4
4.	DESCRIPTION OF THE PROPOSED ACTION	4
	4.1 Requested Approval	4
	4.2 Need for Action	5
	4.3 Location of Production - Environmental Conditions at the Site	5
	4.4 Locations of Use and Disposal of the Drug Product	7
5.	IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION	8
	5.1 Nomenclature	9
	5.1.1 Chemical Names	9
	5.1.2 United States Adopted Names (USAN)	9
	5.2 CAS Registry Numbers	9
	5.3 Structural Formulas	10
	5.4 Molecular Formulas	12
	5.5 Molecular Weights	12
	5.6 Physical Properties	12
	5.6.1 Appearance	12
	5.6.2 Solubility	12
	5.7 Material Safety Data Sheets	13
	5.8 Drug Product Composition	13
6.	INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT	14
	6.1 Substances Generated During Production of Drug Substance	14
	6.2 Substances Generated During Production of Drug Product	15
	6.2.1 Locations of Emission	15
	6.2.2 Environmental Controls-Rouses Point, NY	15
	6.2.3 Environmental Controls-Guayama, Puerto Rico	18

TABLE OF CONTENTS (continued)

Page

6.3 Compliance of Proposed Action With Applicable Emission Requirements . 20

6.3.1 (b) (4) Manufacturer 20
6.3.2 MPA Manufacturers 20
6.3.3 Drug Product Manufacturers 21

6.4 Concentration of Conjugated Estrogens/MPA in the Environment From Product Use 22

6.4.1 Maximum Expected Emitted Concentrations (MEEC) 23

6.5 Concentration of Conjugated Estrogens/MPA in the Environment From Manufacture of the Drug Product 23

7. FATE OF EMITTED SUBSTANCE IN THE ENVIRONMENT 24

7.1 Semi-Continuous Activated Sludge (SCAS) Removability Test 24
7.2 CO_2 Production Tests 25
7.3 Pharmacokinetics of Drug 25
7.4 Transport and Transformation Processes 25

7.4.1 Air 25
7.4.2 Freshwater, Estuary and Marine Ecosystems 25
7.4.3 Terrestrial Ecosystems 26

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES 26

8.1 Acute Toxicity in Aquatic Microorganisms 26
8.2 Acute Toxicity in Mammals 27
8.3 *Potential Toxicity Effects* 27

9. USE OF RESOURCES AND ENERGY 28

10. MITIGATION MEASURES 28

11. ALTERNATIVES TO THE PROPOSED ACTION 29

12. LIST OF PREPARERS 29

TABLE OF CONTENTS (continued)

Page

13. CERTIFICATION 29

14. REFERENCES 30

15. APPENDICES 30

Appendix A Drug Master File Authorization Letters 31
Appendix B Material Safety Data Sheets 34
Appendix C Calculation of Maximum Expected Emitted Concentrations 46
Appendix D Wastewater Treatment Plant Loading 49
Appendix E Five-Year Production Pro Forma 58
Appendix F (b) (4) . . 60
Appendix G . . 144
Appendix H . 288
Appendix I Preparers' Resumes 354
Appendix J Reference Article 359

1. **DATE**

November 6, 1995

2. **NAME OF APPLICANT**

Wyeth-Ayerst Laboratories

3. **ADDRESS**

P.O. Box 8299
Philadelphia, PA 19101-1245

4. **DESCRIPTION OF THE PROPOSED ACTION**

4.1 Requested Approval

Applicant seeks approval of an NDA for the formulation and marketing of conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) combination tablets. Trademark 1 consists of a 0.625 mg CE (b) with either 2.5 or 5.0 mg of MPA. Trademark 2 consists of a 14 day regimen of 0.625 mg CE with no MPA followed by a 14 day regimen containing 0.625 mg CE plus 5.0 mg MPA. The 0.625 mg CE (b) contains a mixture of estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares urine. Medroxyprogesterone acetate is a derivative of progesterone.

CE/MPA therapy is generally indicated in women with an intact uterus, for the treatment of post menopausal symptoms and will be available in mnemonic blister and cycle packages.

Premarin® (conjugated estrogens) has been formulated and marketed since 1942 and to date, no adverse environmental impacts have been observed or reported.

Cycrin® (10 mg MPA) Tablets, have been formulated and marketed since 1987. Cycrin® Tablets containing 2.5 and 5.0 mg MPA were approved in October of 1992. To date, no adverse environmental impacts have been observed or reported.

4.2 Need for Action

Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. The addition of a progestin to an estrogen replacement regimen for more than 10 days per cycle reduces the incidence of endometrial hyperplasia and the attendant risk of adenocarcinoma in woman with intact uteri. The addition of a progestin to an estrogen replacement regimen does not interfere with the efficacy of estrogen replacement therapy.

CE/MPA combination tablets are indicated in women with intact uteri for the treatment of:

1. Moderate to severe vasomotor symptoms associated with menopause.
2. Atrophic vaginitis.
3. Osteoporosis (loss of bone mass).

Estrogen replacement therapy is the most effective single modality for the prevention of osteoporosis in woman.

4.3 Location of Production - Environmental Conditions at the Site

Manufacture of Drug Substances

The active drug substances will be qualified and manufactured at the following sites:

(b) (4)

Wyeth-Ayerst Laboratories
64 Maple Street
Rouses Point, NY 12979

Medroxyprogesterone Acetate (MPA):

(b) (4)

Authorization letters to access the Environmental Assessment sections of the Drug Master Files (DMF) for the (b) (4) facilities identified above are included in Appendix A.

Manufacture of Drug Product

CE/MPA combination tablets may be manufactured, processed, packaged (blisters) and labeled entirely at:

Wyeth-Ayerst Laboratories
64 Maple Street
Rouses Point, NY 12979

The Wyeth-Ayerst facility is located in the northeast corner of New York State near the US-Canadian border. The plant is located on an (b) acre site, with (b) main facilities that consist of (b) buildings that occupy (b) (4) square feet.

The facility is located in the Village of Rouses Point, NY. The land surrounding the facility is of a flat topography. The facility is bordered by Lake Champlain on the east, by a school on the southeast and by a trailer park on the northwest. The area surrounding the Village of Rouses Point can be described as farmland.

(b) (4), branding, packaging (blisters and cycle packs) and labeling may also take place at:

Ayerst-Wyeth Pharmaceuticals, Inc. (AWPI)
State Road No. 3, Km 142.1

The Ayerst-Wyeth (AWPI) plant is located in the southern region of the island Commonwealth of Puerto Rico, approximately 3 kilometers north of the Caribbean Sea and 2 kilometers southwest of Guayama along the north side of State Road No. 3. This region is characteristically warmer and drier than other parts of the island due to the influence of the easterly tradewinds and the proximity of the Cordillera Central to the north. According to the USDA (1977), there is no dry or wet season; however, the period between December through April is drier than the remainder of the year. Heavier rains often occur in May and October.

The area surrounding the plant is typical of a rural industrial setting consisting of lands occupied by sugar cane fields and other manufacturing operations. The plant is bordered on the south by sugar cane fields, on the west by another pharmaceutical facility and a parking lot, on the east by an electrical substation, and on the north by Whitehall Laboratories, another pharmaceutical company which is owned by American Home Products. There are no private residences located near the facility. The facility is located on a (b)(4) acre site, with one main manufacturing building occupying (b) (4) square feet.

All statements made in this report regarding environmental controls, waste management, worker protection, manufacturing processes, use of resources and energy, and training and emergency procedures refer to the drug product formulation and packaging at both the Wyeth-Ayerst facility in Rouses Point, NY and the Ayerst-Wyeth facility in Guayama, Puerto Rico. Authorization letters to access the Environmental Assessment sections of the Drug Master Files (DMF) for the MPA manufacturers are included in Appendix A.

4.4 Locations of Use and Disposal of the Drug Product

As a prescribed treatment for moderate to severe vasomotor symptoms associated with menopause, atrophic vaginitis and osteoporosis, this drug will be distributed to locations throughout the United States for oral administration. The amount that is eliminated or excreted will enter the wastewater stream.

Rejected, outdated or returned goods may be collected, processed and incinerated at:

Wyeth-Ayerst Laboratories
31 Morehall Road
Frazer, PA 19355

(b) (4) may also take place at one of the following locations:

(b) (4)

or the goods may be sent to the following address for (b) (4) :

Wyeth-Ayerst Laboratories
611 E. Nield Street
West Chester, PA 19382

(b) (4) at:

(b) (4)

Rejected, outdated or returned goods may also be collected and processed at:

(b) (4)

for subsequent (b) (4) at:

(b) (4)

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

This NDA is for conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) combination tablets. The active ingredients are identified below.

5.1 Nomenclature

5.1.1 Chemical Names

Conjugated estrogens, USP contains a mixture of estrogens obtained exclusively from natural sources, occurring as the sodium salts of water soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares urine.

Conjugated estrogens contain:

estrone
equilin
17-α-dihydroequilin
17-β-dihydroequilin
17-α-estradiol
(b) (4)

as (b) (4).

Medroxyprogesterone acetate (MPA) is a derivative of progesterone. The chemical name for MPA is:

pregn-4-ene-3,20-dione,17-(acetyloxy)-6-methyl-(6α)-

5.1.2 United States Adopted Names (USAN)

Conjugated Estrogens, USP

Medroxyprogesterone Acetate, USP

5.2 CAS Registry Numbers

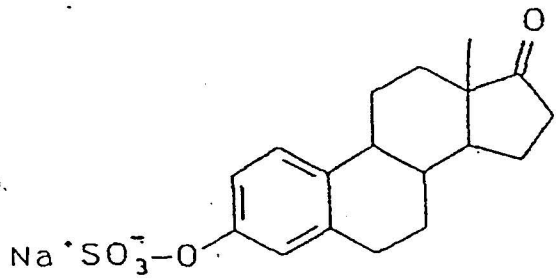
Conjugated Estrogens CAS RN: 12126-59-9

MPA CAS RN: 71-58-9

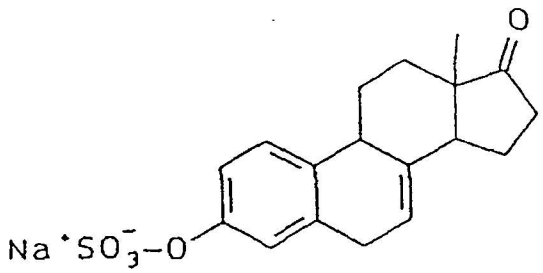
5.3 Structural Formulas

Conjugated Estrogens

Water-soluble estrogen sulfate components

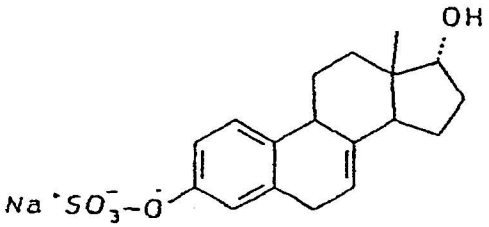


SODIUM ESTRONE SULFATE

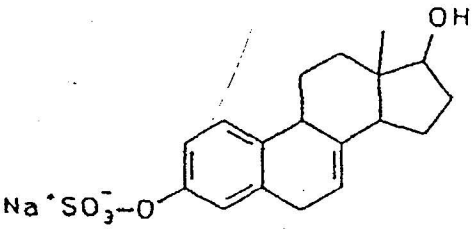


SODIUM EQUILIN SULFATE

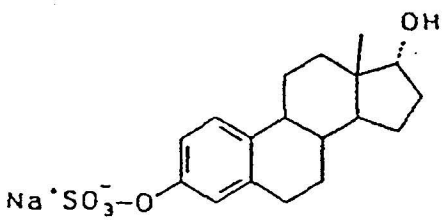
Concomitant Components



SODIUM 17-α-DIHYDROEQUILIN SULFATE



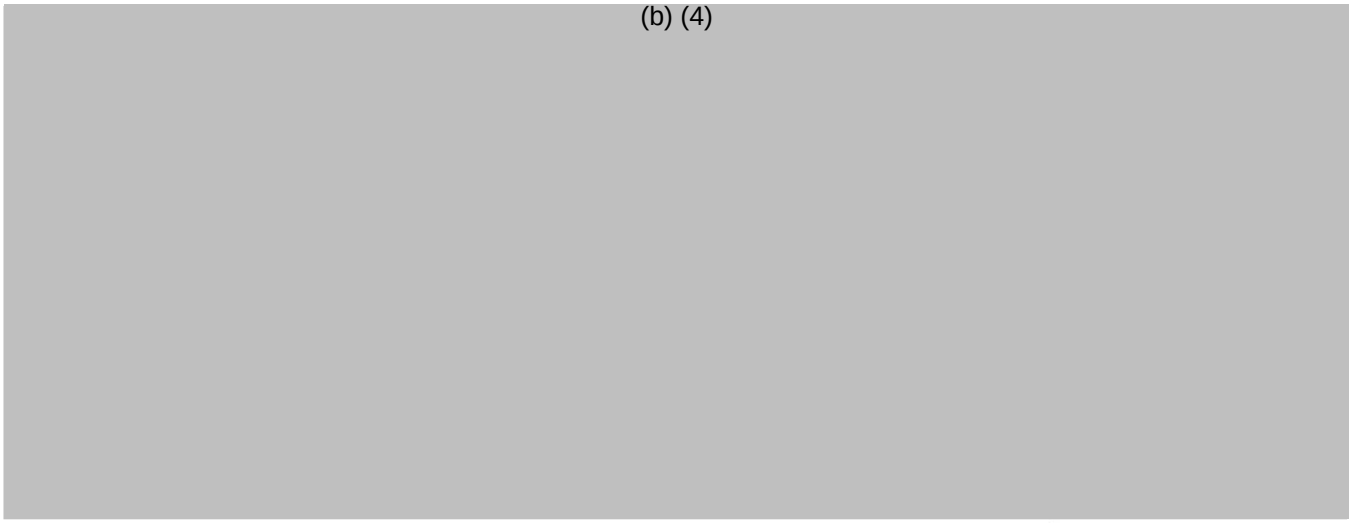
SODIUM 17-β-DIHYDROEQUILIN SULFATE



SODIUM 17-α-ESTRADIOL SULFATE

Other Components

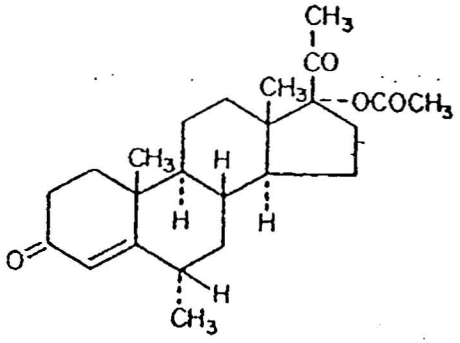
(b) (4)



Signal Impurities

(b) (4)

Medroxyprogesterone Acetate



5.4 Molecular Formulas

Conjugated Estrogens: Varies - See Structural Formulas

MPA: $C_{24}H_{34}O_4$

5.5 Molecular Weights

Conjugated Estrogens: (b) (4)

MPA: 386.53 g/mol

5.6 Physical Properties

5.6.1 Appearance

Conjugated Estrogens: Buff colored amorphous powder

MPA: White to off-white, odorless crystalline powder

5.6.2 Solubility

Conjugated Estrogens: soluble in water @ 25°C

MPA: freely soluble in chloroform
soluble in acetone and dioxane

sparingly soluble in alcohol and methanol
slightly soluble in ether

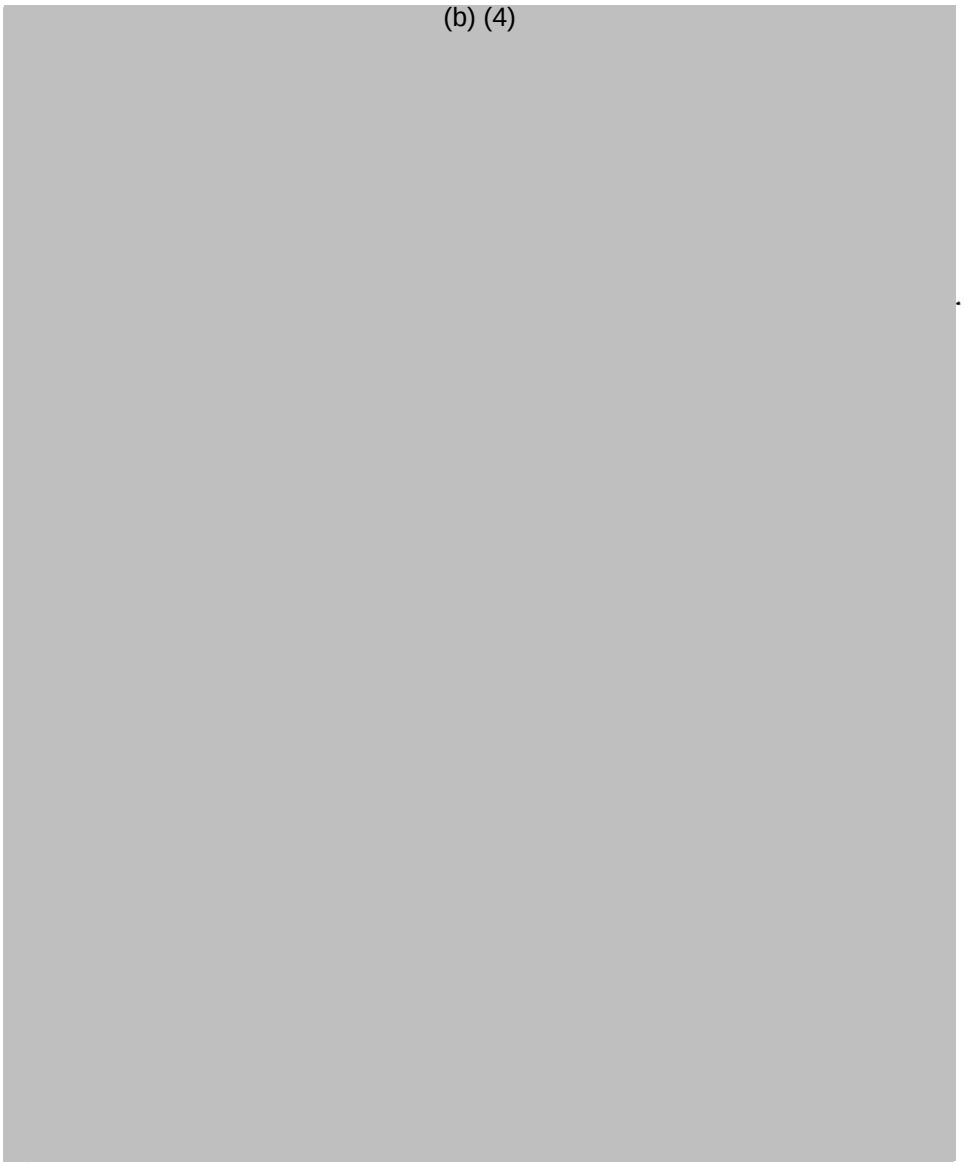
insoluble in water (4.8 μg/mL in water @ 25°C)

5.7 *Material Safety Data Sheets*

The Material Safety Data Sheets for conjugated estrogens and MPA are included in Appendix B.

5.8 Drug Product Composition

(b) (4)



(b) (4)

[redacted]

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1

(b) (4)

[redacted]

(b) (4)

The drug substance manufacturing which takes place at Rouses Point, New York consists of (b) (4) which conforms to USP requirements for conjugated estrogens. Manufacturing controls and permit information for the Rouses Point facility is described in detail in section 6.2.2.

MPA

(b) (4)

(b) (4) in accordance with appropriate laws and regulations. Authorization letters to access the Environmental Assessment sections of the Drug Master Files (DMF) for the MPA manufacturers are included in Appendix A.

6.2 Substances Generated During Production of Drug Product

6.2.1 Locations of Emission

The drug product identified in paragraph 5 may be co-manufactured at the Wyeth-Ayerst facility in Rouses Point, NY and the Ayerst-Wyeth facility in Guayama, Puerto Rico. Both facilities are identified in paragraph 4.3.

6.2.2 Environmental Controls-Rouses Point, NY

Aqueous Waste

(b) (4)

(b) (4)

Air Emission

The following is a summary of process related air emissions, controls, permit numbers and removal efficiencies at the Rouses Point facility. The (b) (4) is the major source of emissions requiring controls. With the exception of (b) (4), similar controls exist at the AWPI facility in Guayama, Puerto Rico.

(b) (4)

(b) (4)

Branding	No significant emissions
Inspection	No significant emissions
Packaging	No significant emissions

Solid Waste

Solid wastes generated during the manufacture of this product consist of the following:

(b) (4)

These wastes will be collected and (b) (4)

(b) (4)

(b) (4)

Pollution Prevention

The facility has in place a pollution prevention program. The participants are actively involved in optimizing production processes, minimizing waste generation and improving waste management practices.

6.2.3 Environmental Controls-Guayama, Puerto Rico

Aqueous Waste

(b) (4)

(b) (4)

The EPA inspects the AWPI wastewater treatment plant annually (at a minimum). This facility is in compliance with its permit which incorporates the effluent guidelines for pharmaceutical mixing/compounding and formulation (40 CFR 439).

Solvent Waste

Recovered solvents are sent to (b) (4)

Air Emission

The (b) (4) is the major source of emissions requiring controls. With the exception of (b) (4)), controls similar to those listed in paragraph 6.2.2 exist at the AWPI facility in Guayama, Puerto Rico. (b) (4) A permit to operate this emission source is granted by the Environmental Quality Board in Guayama, PR. Periodic inspections are conducted by the local authority to ensure all control devices are operated in accordance with the permit parameters.

Solid Wastes

Solid wastes generated during tablet compression and packaging of this product consist of the following:

(b) (4)

These wastes will be collected and (b) (4) at one of the following locations:

(b) (4)

Pollution Prevention

The facility has in place a pollution prevention program. The participants are actively involved in designing the processes for products such as CE/MPA combination tablets.

Addition of this process is not reasonably expected to adversely impact the environment.

6.3 Compliance of Proposed Action With Applicable Emission Requirements

6.3.1

(b) (4)

6.3.2 MPA Manufacturers

(b) (4) identified in paragraph 4.3 are in compliance with all applicable environmental programs. Authorization letters to access the Environmental Assessment sections of

the Drug Master Files (DMF) for these facilities are included in Appendix A.

6.3.3 Drug Product Manufacturers

The pollution control devices and waste disposal methods described in paragraphs 6.2.2 and 6.2.3 serve to minimize environmental emissions from the production of CE/MPA combination tablets.

The Wyeth-Ayerst facility located in Rouses Point, NY and the AWPI facility located in Guayama, Puerto Rico comply with the following federal and state regulations:

Clean Air Act, as Amended

The Wyeth-Ayerst facility in Rouses Point, NY operates under the air permits listed in paragraph 6.2.2. The AWPI facility in Guayama, PR operates under air Permit (b) (4). Addition of this process is not reasonably expected to affect the compliance status of these facilities.

Federal Water Pollution Control Act of 1972, the Clean Water Act, and the Water Quality Act of 1987, as amended

The Rouses Point facility is in compliance with the Village of Rouses Point industrial wastewater permit No. (b) (4) and with the effluent guidelines for pharmaceutical mixing/compounding and formulation (40 CFR 439), as described in paragraph 6.2.2. This facility also operates under NYSDEC storm sewer permit No (b) (4). Addition of this process is not reasonably expected to affect the compliance status of this facility. Please refer to Appendices C and D.

The AWPI facility is in compliance with the state-issued sewage discharge permit No (b) (4) and with the effluent guidelines for pharmaceutical mixing/compounding and formulation (40 CFR 439), as described in paragraph 6.2.3. Addition of this process is not reasonably expected to affect the compliance status of this facility. Please refer to Appendices C and D.

The AWPI facility also holds a permit for (b) (4)

(b) (4) .

Resource Conservation and Recovery Act (RCRA) of 1976 and Amendments of 1984

Solid Waste

These facilities are in compliance with all federal and state regulations governing hazardous waste generators.

(b) (4)

has been examined and determined to be in compliance with the "Ceiling limits" for the constituents addressed by this recently promulgated regulation.

Workplace

Chemicals in the workplace are stored, handled, and managed in accordance with Good Manufacturing Practice (GMP) and OSHA standards. Ventilation, air filtration, personal protection equipment, and industrial hygiene monitoring are employed to ensure containment of chemicals and minimal exposure of workers and the workplace to chemicals. GMP regulations are followed for all equipment and operating procedures.

6.4 Concentration of Conjugated Estrogens/MPA in the Environment From Product Use

Conjugated estrogens and MPA enter the environment in the United States as tablets and through oral administration and subsequent elimination of the drug by human patients.

For purposes of this Environmental Assessment, the parent molecules are used to evaluate environmental release mechanisms and estimated environmental concentrations.

6.4.1 Maximum Expected Emitted Concentrations (MEEC)[1]

The MEEC values are based on fifth year market estimates for the conjugated estrogens/MPA combination tablets. The five year market estimates are included in Appendix E and the MEEC calculations are included in Appendix C.

The MEECs from product use are estimated to be:

(b) (4) mg/L conjugated estrogens

(b) (4) mg/L MPA

6.5 Concentration of Conjugated Estrogens/MPA in the Environment From Manufacture of the Drug Product

Conjugated estrogens/MPA combination tablets will be co-manufactured at the Wyeth-Ayerst facility in Rouses Point, NY and at the Ayerst-Wyeth facility in Guayama, Puerto Rico. The estimated concentrations of conjugated estrogens and MPA emitted during the manufacturing process are based on fifth year production estimates (see Appendix E). Although some product losses occurring during the manufacturing process are suitable for disposal as solid waste, the estimated environmental concentrations are based on a worse case scenario in which all product losses enter the aquatic compartment. Further, the estimated losses from the facility located in Rouses Point, NY assume that the entire drug product is manufactured and packaged at this facility. Based on the above assumptions, the maximum environmental concentrations are estimated as follows:

(b) (4) conjugated estrogens

(b) (4) MPA

The estimated concentrations for the Ayerst-Wyeth facility located in Guayama, Puerto Rico are based on the assumption that final (b) (4) and drug product branding and packaging are conducted at Guayama, Puerto Rico. Thus, the estimates for the Rouses Point facility should be reduced

accordingly. Estimates of the maximum environmental concentrations for the AWPI facility are as follows:

(b) (4) conjugated estrogens

(b) (4) MPA

The wastewater treatment plant loading estimates are included in Appendix D.

7. FATE OF EMITTED SUBSTANCE IN THE ENVIRONMENT

Environmental fate and effects testing was conducted on both MPA and on (b) (4) as described in paragraph 5.8.

7.1 Semi-Continuous Activated Sludge (SCAS) Removability Test

A SCAS test was conducted on both (b) (4) and MPA to determine the removability of the test compound from the aqueous phase of a batch activated sludge system. Activated sludge is exposed to the test substance and the percent soluble organic carbon (SOC) is determined at specific time intervals to estimate the percent soluble carbon removed.

Following a pre-acclimation period, the test substance was added incrementally for a seven-day acclimation period. The final test substance concentrations were (b) (4)) and MPA. Effluents were withdrawn daily during the seven day testing period and analyzed for SOC.

The average percent SOC removal with 95% confidence limits for the test substances are as follows:

(b) (4)) 82.6% ± 1.8%

MPA 90.5% ± 3.5%

Removal mechanisms in a SCAS test may include mineralization of the test substance, sorption to biomass, volatilization or removal by mechanical means. Conjugated estrogens become bioavailable as a result of their solubility in water. Thus, biodegradation is a likely removable mechanism for this test substance. The limited solubility of MPA indicates the removal mechanism was

most likely via mechanical means (centrifugation) during effluent sample preparation.

Copies of these internal reports are included in Appendix F.

7.2 CO_2 Production Tests

The ultimate biodegradation of (b) (4) and MPA were evaluated under aerobic conditions. The systems were analyzed periodically for CO_2 production during a 28 day test period. Greater than 60% of the total CO_2 production for (b) (4)) was observed in only five days, and 100% of the total CO_2 production was observed in eleven days, indicating that (b) (4)) is biodegradable under aerobic conditions. No mineralization of MPA occurred during the same study period as evidenced by -0.4% of CO_2 production.

Copies of these internal reports are included in Appendix G.

7.3 Pharmacokinetics of Drug

The normal recommended daily dosage regimen for this product is 0.625/2.5, 0.625/5.0 or 0.625/0 mg conjugated estrogens/MPA per patient. *Conjugated* estrogens are not expected to be released through patients since the chemical is readily degraded and broken down in the body to metabolites such as estriol, 2-hydroxyestrone, estrone, 16α-hydroxyestrone and estradiol. MPA is not expected to be released through patients, since the chemical is readily degraded and broken down in the body to hydroxylated metabolites and eliminated as glucuronides such as 6,21-dihydroxy-MPA-glucuronide and 2-hydroxy-MPA-glucuronide.

7.4 Transport and Transformation Processes

7.4.1 Air

The (b) (4) is the major source of emissions to the air. As a result of the environmental controls described in paragraph 6.2.2, a limited release of (b) (4) and no active drug substances are expected in this environmental compartment.

7.4.2 Freshwater, Estuary and Marine Ecosystems

Results from the CO_2 production study discussed in paragraph 7.2 show that greater than 60% mineralization (b) (4) occurs in only 5 days. Thus, (b) (4) is considered biodegradable under aerobic conditions. Although the CO_2 production test showed no mineralization of MPA under the same conditions, MPA has a reported biodegradation half life ($t_{1/2}$) of less than 48 hours and is no longer detected after 120 hours (5 days) under aerobic activated biomass type wastewater treatment conditions.[2]

The maximum expected environmental concentrations of conjugated estrogens and MPA at the Rouses Point, NY and Guayama, Puerto Rico facilities were reported in paragraph 6.5. However, since greater than 60% mineralization of (b) (4) and 100% biotransformation of MPA occur in only 5 days, no conjugated estrogens or MPA are expected to persist in the aquatic environment.

7.4.3 Terrestrial Ecosystems

All solid wastes generated from the manufacture of conjugated estrogens/MPA combination tablets are collected and incinerated or landfilled as described in paragraphs 6.2.2 and 6.2.3.

In-house studies also indicate that conjugated estrogens will oxidize in air, undergo acid catalyzed hydrolysis to free phenol and sulfur trioxide in aqueous systems and thermally decompose in the absence of oxygen and at a temperature of 100°C.

Use of conjugated estrogens/MPA combination tablets is not expected to result in the discharge of any toxic material into the environment. Premarin® (conjugated estrogens) has been formulated and marketed since 1942. Cycrin® (10 mg MPA) has been formulated and marketed since 1987 and Cycrin® (2.5 and 5.0 mg MPA) have been approved since October 1992. To date, no adverse environmental impacts have been observed or reported for these products.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Use of this drug product is not expected to result in the discharge of any toxic material into the environment.

8.1 Acute Toxicity in Aquatic Microorganisms

The inhibitory effects of (b) (4) and MPA on aerobic aquatic microorganisms were evaluated by measuring the change in the Dissolved Oxygen (DO) concentration after a three day incubation period. Test concentrations ranged from 1-150 mg Carbon/L for each test substance. No inhibition of microbial activity was observed for (b) (4) or MPA over the concentration range studied when using a D-glucose control. Residual DO values for MPA were nearly identical to those of D-glucose.

Copies of these internal reports are included in Appendix H.

8.2 Acute Toxicity in Mammals

The acute toxicity of conjugated estrogens (CE) was evaluated in mice and rats. The LD_{50} value for mice treated intravenously with CE was 1740 mg/kg. The LD_{50} value for rats treated intraperitoneally with CE was 325 mg/kg.

In studies conducted by Wyeth-Ayerst, the LD_{50} value for CE administered orally and intraperitoneally to male and female CD-1 mice and CD rats was greater than 125 mg/kg.

In studies conducted by Wyeth-Ayerst, the LD_{50} values for CE/MPA (tested in combination) administered orally or intraperitoneally to male and female CD-1 mice or CD rats were greater than 125/1000 mg/kg. Most of the findings in animal studies were due to exaggerated pharmacologic effects of high doses of hormones. The exception is in an MPA rat study where pancreatic tumors were found. In this study, no tumors were found at a dose of 0.2 mg/kg. Tumors were found at dosages of 1 and 5 mg/kg.

8.3 Potential Toxicity Effects

As defined in 21 CFR 25.15(b)(6), a substance is considered toxic in the environment if the maximum concentration of the substance at any point in the environment, i.e., either at any point of entry or any point where higher concentrations are expected as a result of bioaccumulation or other types of concentration processes, exceeds the concentration of the substance that causes any adverse effect in a test organism species (minimum effect level-MEL) or exceeds 1/100 of the concentration that causes 50% mortality in a test organism species (LD_{50} or LC_{50}), whichever concentration is less. This concentration is defined as the "Criterion Concentration" (CC).

One percent of the LD_{50} values for conjugated estrogens (CE) and MPA are conservatively calculated to be 1.25 and 10.00 mg of CE and MPA per kg of body weight respectively. A minimum effect level for MPA was reported as 0.2 mg/kg. Thus, the Criterion Concentration is 1.25 mg/kg for CE and 0.2 mg/kg for MPA based on the acute toxicity studies in mammals. The Criterion Concentration was determined to be greater than 150 mg Carbon/L for both (b) (4) and MPA based on the acute toxicity studies in aquatic microorganisms.

The Maximum Expected Emitted Concentrations from production and product use are summarized in paragraphs 6.4 and 6.5. When human metabolism, biodegradation and biotransformation processes (summarized in paragraph 7) are considered, no conjugated estrogens or MPA are expected in the environment after five days. Thus, the Expected Environmental Concentrations of conjugated estrogens and MPA are less than the Criterion Concentrations, indicating these compounds are not toxic.

9. USE OF RESOURCES AND ENERGY

The Wyeth-Ayerst facility in Rouses Point, NY and the Ayerst-Wyeth facility in Guayama, PR currently manufacture Premarin® (conjugated estrogens) and Cycrin® (MPA) separate tablets. The manufacture and packaging of the conjugated estrogens/MPA combination tablets will require a minimal amount of new process equipment. In addition, market forecasts for the conjugated estrogens/MPA combination tablets reflect some displacement of sales of the existing products. Manufacture of conjugated estrogens/MPA combination tablets will require a relatively insignificant amount (i.e. less than 0.1%) of additional energy and/or resources.

The manufacture of this new drug product will be done within existing facilities at Rouses Point, NY and Guayama, PR. However, renovations were completed to safeguard against employee exposure to MPA (b) (4) at the Rouses Point facility. The (b) (4) was cordoned off by adding ceilings and cement walls. A negative air pressure is also supplied to the room to prevent the release of MPA.

Approval of the NDA will have no effect upon endangered or threatened species or property listed in or eligible for listing in the National Register of Historic Places.

10. MITIGATION MEASURES

All drug product manufacturing facilities have taken measures (described in Section 6) to achieve compliance with the regulations governing the proposed manufacture of conjugated estrogens /MPA combination tablets.

Emissions of the drug product to the air are controlled by high efficieny control equipment described in Section 6. Emissions of the drug product to wastewater are controlled by either (b) (4) prior to treatment at a publically owned treatment facility, or by onsite treatment which includes activated sludge treatment with ozonation. Emissions to the land do not occur because all solid waste generated during manufacturing is incinerated as described in Section 6.

In addition to air, wastewater and waste control measures previously discussed, all responses to hazardous materials emergencies are governed by plant emergency response procedures. All operations are conducted in a manner which minimizes the potential for environmental incidents and are in compliance with emergency preparedness and prevention requirements.

11. ALTERNATIVES TO THE PROPOSED ACTION

Due to the lack of environmental impact of the proposed product, no alternative actions are proposed.

12. LIST OF PREPARERS

Diane L. Smith, Ph.D.
Environmental Scientist
Wyeth-Ayerst Laboratories

Mr. Craig F. Seyfried
Associate Director - Environmental Control
Wyeth-Ayerst Laboratories

The preparers' resumes are provided in Appendix I.

13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for preparation of this environmental assessment.

CERTIFIED BY: Craig F. Seyfried

Craig F. Seyfried
Associate Director - Env. Control

DATE: Nov 7, 1995

14. REFERENCES

1. Pharmaceutical Manufacturers Association, *Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA,* July 1991.

2. K. Norpoth, A. Nehrkorn, M. Kirchner, H. Holsen and H. Teipel; (2b1.) Bakt. Hyg., I Abr. Orig. 13156, *Investigations on the Problem of Solubility and Stability of Steroid Ovulation Inhibitors in Water, Wastewater and Activated Sludge*; 1973, p 500-511. (Included in Appendix J)

3. Wyeth-Ayerst Standard Operating Practice and Batch Records; Premarin®.

4. Wyeth-Ayerst Communications; Excerpt from Draft Premarin®/MPA Direction Circular.

15. APPENDICES

Appendix A Drug Master File Authorization Letters

Appendix B Material Safety Data Sheets

Appendix C Calculation of Maximum Expected Emitted Concentrations

Appendix D Wastewater Treatment Plant Loading

Appendix E Five-Year Production Pro Forma

Appendix F (b) (4)

Appendix G

Appendix H

Appendix I Preparers' Resumes

Appendix J Reference Article

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

/s/

Nancy Sager
7/15/02 10:16:59 AM
This electronic signature denotes when the FONSI was archived into the electronic division file system (DFS). See the document for original signatures and approval date.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-527/S-024, S-026, S-031

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	20-527/S-024
Name of drug:	Prempro™ (Conjugated Estrogens/Medroxyprogesterone Acetate Tablets)
	Premphase® (Conjugated Estrogens/Medroxyprogesterone Acetate Tablets)
Strength	0.3 mg CE / 1.5 mg MPA
Applicant:	Wyeth-Ayerst Laboratories.
Indication:	1. Treatment of moderate to severe vasomotor symptoms associated with menopause
	2. Treatment of vulvar and vaginal atrophy associated with the menopause
Documents reviewed:	\\CDSESUB1\N20527\S_024\2001-11-05
Project manager:	Dornette Spell-LeSANE
Clinical reviewer:	Theresa H. van der Vlugt, M.D., M.P.H.
Dates:	Received 11/5/01; user fee 9/7/02; division goal 6/30/02
Statistical reviewer:	Moh-Jee Ng, M.S.
Statistics team leader:	Michael Welch, Ph.D.
Biometrics division director:	S. Edward Nevius, Ph.D.

Keywords: NDA review, clinical studies, analysis of covariance

1. INTRODUCTION AND BACKGROUND

Prempro™/Premphase® (conjugated estrogens (CE) and medroxyprogesterone acetate (MPA)) has been approved by FDA at doses of 0.625 mg CE/2.5 mg MPA, 0.625 mg CE/5 mg MPA, for the treatment of moderate-to-severe vasomotor symptoms (MSVS), treatment of vulvar and vaginal atrophy (VVA), and protection of the endometrium. On April 13, 2001, the 0.45 mg CE/1.5 mg MPA dosage strength received an approvable action for MSVS and VVA, and protection of the endometrium. However, a lower dose of 0.3 mg CE /1.5 mg MPA was withdrawn without prejudice because there were three concerns:

1. Efficacy of this strength for the subgroup of women close to menopause (< 50 years of age)
2. The number of breast cancers found in this dosage group, and
3. A less favorable lipid profile.

In this supplement NDA, the sponsor included a single 2-year trial to address these concerns. However, this review focuses on lipid profile as requested by the medical reviewer because the first two concerns have been addressed in the medical review.

In this submission, the sponsor presented one clinical trial - 0713D2-309-US - the Health and Osteoporosis, Progestin and Estrogen Study (HOPE). It is an 8-arm, placebo-controlled, double-blind, placebo/active-drug-controlled, multicenter clinical study conducted in healthy postmenopausal women with an intact uterus. Table 1 summarizes the study:

Table 1
Summary of Controlled Trial

Study Number	Study Design	Treatment Group	Sample Size	Duration of Treatment
0713D2-309-US	Basic study, double-blind, multicenter, randomized placebo/active-drug controlled	A: 0.625 mg CE	348	1 year
		B: 0.625 mg CE / 2.5 mg MPA	331	
		C: 0.45 mg CE	338	
		D: 0.45 mg CE / 2.5 mg MPA	340	
		E: 0.45 mg CE / 1.5 mg MPA	331	
		F: 0.3 mg CE	326	
		G: 0.3 mg CE/1.5 mg MPA	327	
		H: Placebo	332	
0713D2-309-US	Substudy, double-blind, randomized, multicenter, placebo/active-drug controlled	A: 0.625 mg CE	97	2 years
		B: 0.625 mg CE / 2.5 mg MPA	86	
		C: 0.45 mg CE	95	
		D: 0.45 mg CE / 2.5 mg MPA	96	
		E: 0.45 mg CE / 1.5 mg MPA	94	
		F: 0.3 mg CE	89	
		G: 0.3 mg CE/1.5 mg MPA	98	
		H: Placebo	94	

This study contains two parts, a "basic" study and a "substudy". The "basic" study is year 1 of the HOPE study; a total of 2,673 subjects were randomized to 8 treatment groups. The "substudy" is study year 1 and2 and consisted of 749 of the 2,673 original

enrolled. The primary objective of the substudy was to measure bone loss due to osteoporosis (refer to statistical review of NDA 21396).

Demographic and baseline characteristics were similar among all the treatment groups in the metabolic substudy. A total of 230 (31%) of 749 subjects withdrew from the study. 21% in the 0.3 mg CE/1.5 mg MPA and 34% in the placebo group did not complete the study. The drop out rate is high in this substudy.

2. DATA ANALYZED AND SOURCES

SAS data sets were provided by the sponsor in the electronic submission.

3. STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY

This reviewer only analyzed the lipid profiles. Please refer to Medical review regarding the relief of vasomotor symptoms (refer to statistical review of NDA 20,527/S-017, DFS date 3/18/2001), vaginal maturation index, bleeding profiles, incidence of amenorrhea, reducing the incidence of endometrial hyperplasia (refer to statistical review of NDA 20,527/S-017, DFS date 3/18/2001), or cancer.

3.1 SPONSOR'S RESULTS AND CONCLUSIONS OF LIPID EFFECTS

The lipid data were evaluated by analysis of variance (ANOVA) based on mean percent changes from baseline at cycles 6, 13, 19 and 26, with treatment and site effect included. Baseline values were determined by the average of the last 2 values prior to study medication intake – approximately 7 to 14 days apart. The sponsor also performed pairwise comparisons of each active treatment group to the placebo group. All efficacy analyses are based on an intent-to-treat (ITT) population, with last observed carried forward (LOCF). The ITT is defined as all subjects randomized in the substudy who completed at least one cycle of study medication. The minimum number of subjects in each treatment group with lipid data at the baseline and cycles 6, 13, 19, and 26 list as below:

- 0.3 mg CE/1.5 mg MPA (baseline: 98; cycle 6: 89; cycle 13: 80; cycle19: 75; cycle 26: 72)
- Placebo (baseline: 93; cycle 6: 83; cycle 13: 77; cycle19: 62; cycle 26: 59)

(b) (4)

3.2 STATISTICAL EVALUATION OF LIPID EFFECTS

Table 2 summarizes the result comparing 0.3 mg CE/1.5 mg MPA with placebo. The number of subjects in each treatment group with lipid data at cycles 6, 13, 19, and 26 list as below:

- 0.3 mg CE/1.5 mg MPA (cycle 6: **89**; cycle 13: **81**; cycle19: **75**; cycle 26: **74**)
- Placebo (cycle 6: **84**; cycle 13: **78**; cycle19: **63**; cycle 26: **60**)

Table 2
Summary Lipid Effects

Total cholesterol	• Statistically significant mean percent increases in 0.3 mg CE/1.5 mg MPA at cycle 6 • No statistically significant differences between these two treatment groups
HDL-cholesterol	• Statistically significant mean percent increases in 0.3 mg CE/1.5 mg MPA at all cycles • Statistically significant difference between 0.3 mg CE/1.5 mg MPA and placebo at cycle 19
HDL_2-cholesterol	• Statistically significant mean percent increases in 0.3 mg CE/1.5 mg MPA at all cycles • Statistically significant differences between 0.3 mg CE/1.5 mg MPA and placebo at cycles 6 and 26
LDL-cholesterol	• Statistically significant mean percent decreases in 0.3 mg CE/1.5 mg MPA at cycles 6 and 19 • Statistically significant differences between 0.3 mg CE/1.5 mg MPA and placebo at all cycles
VLDL-cholesterol	• Statistically significant mean percent increases in 0.3 mg CE/1.5 mg MPA at cycles 6, 13 and 19 • No statistically significant differences between these two treatment groups
LDL-C/HDL-C	• Statistically significant mean percent decreases in 0.3 mg CE/1.5 mg MPA at all cycles • Statistically significant differences between 0.3 mg CE/1.5 mg MPA and placebo at all cycles
Triglycerides	• Statistically significant mean percent increases in 0.3 mg CE/1.5 mg MPA at all cycles • No statistically significant differences between these two treatment groups

There were statistically significant differences between 0.3 mg CE/1.5 mg MPA and placebo groups in LDL cholesterol, and LDL-C/HDL-C ratios at all cycles. There were statistically significant differences in HDL cholesterol at cycle 19 and HDL_2 cholesterol at cycles 6 and 26. There were no statistically significant differences in total cholesterol, VLDL cholesterol and triglycerides. Note that increases in the HDL cholesterol, HDL_2 cholesterol and decreasing LDL cholesterol are beneficial effects.

Table 3
Mean Percent Change from Baseline of Lipid Profile
ITT population

		Prempro 0.3mg CE/1.5 mg MPA			Placebo			
	Time Period	Mean (SD)	Mean Percent Change from baseline (SD)	P-values Within Group	Mean (SD)	Mean Percent Change from baseline (SD)	P-values Within Group	P-values Versus Placebo
Total -C	Cylce 6	5.5 (.9)	-.4 (1.1)	0.65	5.6 (.9)	1.3 (1.1)	.23	0.24
	Cycle 13	5.4 (.9)	1.6 (1.2)	0.14	5.5 (.9)	3.1(1.2)	0.006	0.35
	Cycle 19	5.4 (.9)	-.2 (1.2)	0.88	5.5 (.9)	3.2 (1.3)	0.005	0.057
	Cycle 26	5.4 (.9)	2.9 (1.3)	0.015	5.5 (.9)	5.7 (1.4)	<0.001	0.15
HDL-C	Cylce 6	1.4 (.3)	5.4 (1.4)	<.001	1.5 (.3)	2.3 (1.5)	0.095	0.12
	Cycle 13	1.4 (.3)	5.5 (1.6)	<.001	1.5 (.4)	2.0 (1.6)	0.12	0.12
	Cycle 19	1.4 (.3)	7.2 (1.7)	<.001	1.5 (.4)	2.3 (1.9)	0.12	0.049
	Cycle 26	1.4 (.3)	8.5 (1.8)	<.001	1.5 (.4)	3.8 (1.9)	0.035	0.068
HDL_2-C	Cylce 6	.4 (.2)	21.9 (5.6)	<.001	.4 (.2)	2.5 (5.8)	0.48	0.014
	Cycle 13	.4 (.2)	18.3 (5.6)	<.001	.4 (.2)	3.9 (5.8)	0.29	0.071
	Cycle 19	.4 (.3)	23.6 (6.1)	<.001	.4 (.3)	6.9 (6.6)	0.22	0.060
	Cycle 26	.4 (.2)	23.9 (6.2)	<.001	.4 (.3)	4.8 (7.0)	0.40	0.035
LDL-C	Cylce 6	3.5 (.9)	-4.6 (1.4)	0.001	3.6 (.8)	-.2 (1.5)	0.89	0.025
	Cycle 13	3.5 (.9)	-1.8 (1.5)	0.33	3.6 (.8)	3.0 (1.5)	0.038	0.024
	Cycle 19	3.5 (.9)	-4.7 (1.6)	0.006	3.6 (.8)	3.7 (1.7)	0.012	<0.001
	Cycle 26	3.5 (.9)	-.5 (1.8)	0.99	3.6 (.8)	7.1 (2.0)	<0.001	0.004
VLDL-C	Cylce 6	.5 (.5)	22.2 (10.6)	0.027	.5 (.3)	22.7 (11)	0.024	0.97
	Cycle 13	.5 (.5)	31.0 (11.2)	0.005	.4 (.3)	22.5 (11.6)	0.038	0.59
	Cycle 19	.5 (.5)	23.7 (11.4)	0.028	.5 (.3)	20.6 (12.4)	0.057	0.07
	Cycle 26	.5 (.5)	23.3 (15)	0.063	.5 (.3)	17.2 (16.6)	0.16	0.49
LDL-C /HDL-C	Cylce 6	2.7(.9)	-9.1 (1.5)	<.001	2.6 (.8)	-2.0 (1.6)	0.16	0.001
	Cycle 13	2.6 (.9)	-6.0 (1.7)	<.001	2.6 (.8)	1.6 (1.7)	0.44	0.002
	Cycle 19	2.6 (.9)	-10.7 (1.7)	<.001	2.6 (.9)	2.2 (1.9)	0.22	<0.001
	Cycle 26	2.5 (.9)	-7.6 (1.9)	<.001	2.6 (.9)	3.3 (2.0)	0.087	<0.001
Triglycerides	Cylce 6	1.3 (.8)	17.5 (4.8)	<.001	1.3 (.6)	9.8 (5.0)	0.039	0.26
	Cycle 13	1.2 (.7)	23.3 (5.2)	<.001	1.3 (.6)	10.7 (5.4)	0.063	0.088
	Cycle 19	1.2 (.8)	20.3 (6.1)	.001	1.3 (.6)	6.8 (6.6)	0.25	0.13
	Cycle 26	1.2 (.7)	21.6 (5.8)	<.001	1.3 (.6)	5.5 (6.3)	0.31	0.055

Source: Table ST11-20 Summary tabulation of Lipids Percent Change from Baseline within and between Groups

4. LABELING COMMENTS

(b) (4)

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Mike Welch
6/17/02 04:09:03 PM
BIOMETRICS
Concur with review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-527/S-024, S-026, S-031

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	**20-527 SLR-017**
Compound:	0.45 or 0.3 mg conjugated estrogens and 1.5 mg medroxyprogesterone acetate
Sponsor:	Wyeth-Ayerst Research
Type of Submission:	Efficacy Supplement
Submission Dates:	**20-527 SLR-017, June 15, 2000; SE2-017-BB: October 24, 2000 and February 28, 2001; SE2-017-BC: April 11, 2001 and April 12, 2001; SE2-017-BL: April 11, 2001; SE2-017-C: April 12, 2001.**
Reviewer:	S.W. Johnny Lau, R.Ph., Ph.D.

Synopsis:

NDA 20-527 SLR-017 (IND 21,696) proposes 2 oral tablets, 0.45 mg conjugated estrogens (CE)/1.5 mg medroxyprogesterone acetate (MPA) or 0.3 mg CE/1.5 mg MPA, in a continuous combined regimen for the treatment of moderate to severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy was submitted on June 15, 2000.

Sponsor conducted a clinical safety and efficacy study (0713D2-309-US; Health and Osteoporosis, Progestin and Estrogen (HOPE) study for CE and MPA) to support NDA 20-527 SLR-017. Sponsor conducted 2 relative bioavailability studies (0713D2-119-US and 0713D2-120-US) to support the Human Pharmacokinetics and Bioavailability section of NDA 20-527 SLR-017. These 2 studies are identical in design (randomized, single-dose, 4-period/treatment, crossover) except different CE and MPA combination strengths were administered. Study 0713D2-119-US concerns 2 x 0.625 mg CE/2.5 mg MPA, 2 x 0.45 mg CE/2.5 mg MPA, 2 x 0.45 mg CE/1.5 mg MPA, and 2 x 0.45 mg CE alone oral tablets. Whereas, Study 0713D2-120-US concerns 2 x 0.625 mg CE/2.5 mg MPA, 2 x 0.45 mg CE/1.5 mg MPA, 2 x 0.3 mg CE/1.5 mg MPA, and 2 x 0.3 mg CE alone oral tablets. The formulations (CE/MPA and CE) tested in the clinical Studies 0713D2-309-US, 0713D2-119-US, and 0713D2-120-US are identical to the market formulations in terms of scale of manufacture and composition except the color coat, which was white in the clinical formulations. This color change between the clinical batch and to-be-marketed batch was justified via in vitro dissolution data.

Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB DPEII) has reviewed NDA 20-527 SLR-017 dated June 15, 2000. OCPB finds that the submitted information supports the Human Pharmacokinetics and Bioavailability section of NDA 20-527 SLR-017.

- Sponsor's proposed conjugated estrogens in vitro dissolution method (USP XXIV apparatus 2, 900 mL water, 37°C, and 50 rpm) is acceptable. However, the recommended conjugated estrogens in vitro dissolution specifications for the 0.45 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate and 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate oral tablets are:

Time	% estrone sulfate released
2 hours	Not more than (b)
5 hours	(b) (4))
8 hours	Not less than (b)

Sponsor accepted the recommended conjugated estrogens in vitro dissolution specifications per sponsor's April 12, 2001 letter.

- Sponsor's proposed medroxyprogesterone acetate in vitro dissolution method via USP disintegration apparatus (0.54% sodium lauryl sulfate, 900 mL, 37°C, and 30 dips/min) is acceptable on an interim basis. The recommended medroxyprogesterone acetate specification for the 0.45 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate and 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate oral tablets are:

Time	% medroxyprogesterone acetate released

30 minutes	Not less than (b) (Q = (b))

Sponsor accepted the recommended medroxyprogesterone acetate in vitro dissolution specifications per sponsor's April 11, 2001 letter.

- Sponsor should develop the medroxyprogesterone acetate dissolution methods via the USP in vitro dissolution apparatuses (such as basket and paddle) for the 0.45 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate and 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate tablets as well as the other approved strengths of conjugated estrogens and medroxyprogesterone acetate tablets as a Phase IV commitment. The final dissolution specifications for the medroxyprogesterone acetate components of the 0.45 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate and 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate tablets will be based on data via the USP in vitro dissolution apparatus. Per sponsor's April 12, 2001 letter, sponsor is committed to in vitro dissolution feasibility study via the (b) (4) and provide the FDA with the new in vitro dissolution method and preliminary data for comments approximately 4 months after approval.
- Sponsor's Clinical Pharmacology labeling changes per teleconference on April 12, 2001 are accepatble.

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

An Optional Intra-Division Clinical Pharmacology and Biopharmaceutics Briefing for NDA 20-527 SLR-017 was conducted on March 19, 2001; participants included D. Moore, D. Lin, H. Malinowski, J. Hunt, A. Parekh, and J. Lau.

FT signed by Ameeta Parekh, Ph.D., Team Leader 4/ /01

cc: NDA 20-527, HFD-870 (H. Malinowski, A. Parekh, J. Lau), HFD-580 (T. van der Vlugt, D. Moore), HFD-820 (D. Lin), CDR (B. Murphy for Drugs)

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Ameeta Parekh
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-527/S-024, S-026, S-031

OTHER REVIEW(S)

Division of Reproductive and Urologic Drug Products

ADMINISTRATIVE REVIEW OF APPLICATION

Application Number: **20-527/S-024**

Name of Drug: Prempro™/Premphase® (0.3 mg/1.5 mg)

Sponsor: Wyeth-Ayerst Laboratories, Inc.

Material Reviewed: Supplement-024

Submission Date: November 5, 2001

Receipt Date: November 7, 2001

Filing Date: January 7, 2002

User-Fee Goal Date: September 7, 2002

Proposed Indication: Relief of moderate-to-severe vasomotor symptoms and treatment of vulvar and vaginal atrophy

Other Background Information: NDA 20-303; NDA 20-527, NDA 4-782,

Review

PART I: OVERALL FORMATTING[a]

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

	Y	N	COMMENTS (list volume & page numbers)
1. Cover Letter (original signature)	X		Volume 1
2. Form FDA 356h (original signature)	X		Volume 1
a. Reference to DMF(s) & Other Applications	X		In cover letter
3. Patent information & certification	X		CD Rom, other
4. Debarment certification (note: must have a definitive statement)	X		CD Rom, other
5. Financial Disclosure	X		CD Rom, other

6. Comprehensive Index	X		CD Rom, Main 309
7. Pagination	X		Entire submission
8. Summary Volume			
9. Review Volumes	X		CD Rom
10. Labeling (PI, container, & carton labels)	X		Volumes 2, CD Rom, 309 Main
a. unannotated PI	X		Volumes 2, CD Rom, 309 Main
b. annotated PI		X	
c. immediate container	X		Volumes 2, CD Rom, 309 Main
d. carton	X		Volumes 2, CD Rom, 309 Main
e. foreign labeling (English translation)		X	
11. Foreign Marketing History		X	
12. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		CD Rom, crt
13. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		CD Rom, crf

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

PART II: SUMMARY[b]

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

	Y	N	COMMENTS (list volume & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits		X	Referenced to NDA 20-303 Volume 1.6 and 1.5-1.7
2. Summary of Each Technical Section	X		
a. Chemistry, Manufacturing, & Controls (CMC)	X		CD Rom Main page 45
b. Nonclinical Pharmacology/Toxicology		X	Referenced to NDA 20-303 Volume 1.6 and 1.5-1.7 Not applicable as this drug product is already approved at higher dosage strengths
c. Human Pharmacokinetic & Bioavailability	X		CD Rom Main page 76
d. Microbiology		X	Not applicable
e. Clinical Data & Results of Statistical Analysis	X		CD Rom Main page 78
3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		CD Rom Main page 242
4. Summary of Safety	X		CD Rom 309 Main Item 10
5. Summary of Efficacy	X		CD Rom 309 Main Item 9

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

PART III: CLINICAL/STATISTICAL SECTIONS[c]

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

	Y	N	COMMENTS (list volume & page numbers)
1. List of Investigators	X		CD Rom clinstat\other\listof investigators.pdf
2. Controlled Clinical Studies	X		CD Rom clinstat.pdf
a. Table of all studies	X		CD Rom clinstat\other\listof investigators.pdf
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		Volume 10, 8-1 through 8-43
c. Optional overall summary & evaluation of data from controlled clinical studies	X		Volume 10, 8-1 through 8-8
3. Integrated Summary of Efficacy (ISE)		X	
4. Integrated Summary of Safety (ISS)		X	
5. Drug Abuse & Overdosage Information	X		CD Rom clinstat\other\listof investigators.pdf
6. Integrated Summary of Benefits & Risks of the Drug	X		CD Rom clinstat\other\listof investigators.pdf
7. Gender/Race/Age Safety & Efficacy Analysis Studies		X	

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

PART IV: MISCELLANEOUS

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

	Y	N	COMMENTS (list volume & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population	X		Requested a waiver for pediatric population
2. Diskettes	X		EDR
a. Proposed unannotated labeling in MS WORD 8.0	X		Volume 1
b. Stability data in SAS data set format		X	
c. Efficacy data in SAS data set format		X	
d. Biopharmacological information & study summaries in MS WORD 8.0		X	
e. Animal tumorigenicity study data in SAS data set format		X	
3. User-fee payment receipt	X		Volume 1, CD Rom, clinstat\other

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

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

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

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

Additional Comments:

Conclusions: This efficacy supplement references data from previously approved NDA supplements and bioequivalence studies. The supplement can be filed from a regulatory perspective.

_____

Regulatory Health Project Manager

_____

Concurrence

cc:

Original NDA
HFD-580/Div. Files
HFD-580/PM/D.Moore
HFD-580/S.Allen/D.Shames
HFD-580/S.Slaughter/P.Price/M.Rhee/A.Mitra/A.Jordan/K.Raheja/A.Parekh/V.Jarugula
draft: May 14, 2001
final: May 15, 2001

ADMINISTRATIVE REVIEW

Drug Abuse and Overdosage

Serious ill effects have not been reported following acute ingestion of large doses of estrogen/progestin-containing oral contraceptives by young children. Overdosage may cause nausea and vomiting, and withdrawal bleeding may occur in females.

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

DDMAC Review

Labeling comments were incorporated into the labeling on the Division "N" drive following discussions in the labeling meetings.

4 Page(s) Withheld

X Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

Abuse Liability review

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

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

Microbiology Review

No Microbiology review was performed for this supplemental efficacy application because microbiology efficacy does not pertain to this product. No preservative challenge is conducted for these tablet formulations.

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

DSI Audit of Clinical Studies

It was determined at the filing meeting that a DSI inspection was not warranted for this supplement because the drug is already approved for higher dosages.

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

Safety Update Review

The safety update review is in the Medical Officer's review dated 6/4/02~~2001~~.

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

End of Phase 2 and Pre-NDA meetings

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

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

Advisory Committee Meeting Minutes

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

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

Federal Register Notices

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

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

Division Director's Memo

The application will be signed off at the Division level. No memo is necessary.

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

Group Leader's Memo

No Group Leader's memo will be prepared; the memo will be prepared by the Division Director; no Group Leader memo is required.

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth Laboratories, Inc.

Trademark Review

Trademark review was not required for this supplement.

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

Advertising Material

No advertising material has been submitted.

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

Post-Marketing Commitments

No post-marketing commitments were made for this Supplement.

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

Statistical Review Regarding Dissolution and/or Stability

No statistical review regarding dissolution and/or stability was requested.

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

Environmental Assessment

A categorical exclusion is claimed for this NDA in accordance with 21 CFR part 25.31 (b), as amended in the 29-Jul-1997 Federal Register. This was found to be satisfactory (see Chemistry Review dated , 2001).

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

Micro (validation of sterilization) review

No microbiology validation review is required for tablets.

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

EER

See Chemistry Review dated 5/7/~~2001~~ 02.

NDA 20-527

Prempro™ / Premphase®
Conjugated Estrogens and Medroxyprogesterone Acetate Combination Tablets

Prempro™ 0.3/1.5

Indications
Vasomotor Symptoms, and Vulvar and Vaginal Atrophy

Item 17: Certification Required by the New Drug and Abbreviated New Drug Applications Pre-approval Inspection Requirements

As required under 21CFR §314.50 (d)(1)(v), the undersigned certifies that Wyeth-Ayerst has provided a true copy of the Chemistry, Manufacturing and Controls section, the application form and the application summary of sNDA 20-527 for Prempro™ / Premphase® (conjugated estrogens/medroxyprogesterone acetate tablets) 0.3mg/1.5mg strength, to the Buffalo, New York and San Juan, Puerto Rico manufacturing District Offices of the FDA. The Philadelphia District Office, the FDA home office for Wyeth-Ayerst, has been notified (by mail) that these copies have been sent.

Signature _____

Joseph Sonk, Ph. D.
Assistant Vice President
Worldwide Regulatory Affairs

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

Methods Validation

The methods validation for this product have been completed and are acceptable (see Chemistry review dated 8/21/02, ~~2001~~).

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

DSI memo regarding GLP inspection

No GLP inspection was required for this efficacy supplemental application.

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

Statistical Review of Carcinogenicity Studies

No statistical review was performed because higher dosage strengths of this product have been previously approved.

NDA 20-527/S-024
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

CAC/ECAC report

No CAC/ECAC report was made for this efficacy supplemental application because higher dosage strengths have previously been approved.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-527/S-024, S-026, S-031

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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:	PREMPRO®
Active Ingredient(s):	conjugated estrogens and medroxyprogesterone acetate
Strength(s):	(1) 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

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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.
Patent Counsel
Date: 6/18/01

Amended Patent / Exclusivity Information

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

Amended Patent / Exclusivity Information

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

EXCLUSIVITY SUMMARY for NDA # 20-527 SUPPL # 024

Trade Name Prempro/Premphase Generic Name conjugated estrogens/medroxyprogesterone acetate)

Applicant Name Wyeth Pharmaceuticals

HFD-580

Approval Date June 9, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA? YES/ __ / NO /_✔__/

   b) Is it an effectiveness supplement? YES /_✔__/ NO /___/

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

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

      YES /_✔__/ NO /___/

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

      _____

      _____

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

      _____

      _____

d) Did the applicant request exclusivity?

YES /___/ NO /_✓__/

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

_____

_____

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

YES /___/ NO /_✓__/

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

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

YES /___/ NO /_✓__/

If yes, NDA # _____ Drug Name _____

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

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

YES /___/ NO /_✓__/

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

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

1. Single active ingredient product.

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

YES /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

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

YES /_✓__/ NO /___/

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

NDA # 20-527 Prempro/Premphase

NDA # _____ _____

NDA # _____ _____

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

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

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

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

YES /✔___/ NO /___/

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

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

YES /_✓__/ NO /___/

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

_____

_____

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

YES /__✓_/ NO /___/

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

YES /___/ NO /_✓__/

If yes, explain: _____

_____

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

YES /___/ NO /_✓__/

If yes, explain: _____

_____

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

Investigation #1, Study # 0713D2-309-US_____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

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

Investigation #1	YES /_✓__/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

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

NDA # 20-527 Study # 0713D2-309-US

NDA # _____ Study # _____

NDA # _____ Study # _____

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

Investigation #1 YES /___/ NO /_✓__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

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

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

Investigation #1

IND # 21,696 YES /✓/ NO /___/ Explain: _____

_____

_____

Investigation #2

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

_____

_____

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

Investigation #1

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

_____ _____

_____ _____

Investigation #2

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

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /__✓_/

If yes, explain: _____

_____

_____

Kassandra Sherrod,R.Ph. 5/6/03

Signature of Preparer Date

Title:Regulatory Project Manager_

_____ _____

Signature of Office or Division Director Date

cc:
Archival NDA
HFD-580/Division File
HFD-580/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 20-527 Supplement Type (e.g. SE5): SE2 Supplement Number: 024

Stamp Date: November 7, 2001 Action Date: June 4, 2003

HFD 580 Trade and generic names/dosage form: PREMPRO™ PREMPHASE®(conjugated estrogens/medroxyprogesterone acetate tablets)

Applicant: Wyeth Pharmaceuticals Therapeutic Class: hormone therapy

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Treatment of moderate to severe vasomotor symptoms associated with the menopause

Is there a full waiver for this indication (check one)?

×Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
×Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed

☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

Is there a full waiver for this indication (check one)?

×Yes: Please proceed to Section A.

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
×Disease/condition does not exist in children
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

/s/

Kassandra C. Sherrod
6/12/03 09:32:23 AM

N020527
Prempro™/ Premphase®
Conjugated Estrogens / Medroxyprogesterone Acetate Tablets

Lower Dose of Prempro™ 0.3mg/1.5mg

Item 20: Pediatric Rule (Waiver Requested)

In accordance with 21 CFR §314.55, Wyeth-Ayerst believes that pediatric data is not required for inclusion within this application. This application is for the addition of a lower dose of previously approved Prempro™ /Premphase® products that are indicated for postmenopausal symptoms, i.e., treatment of vasomotor symptoms, treatment of vulvar and vaginal atrophy and the prevention of osteoporosis. This product is not indicated for any pediatric population.

Signature _____

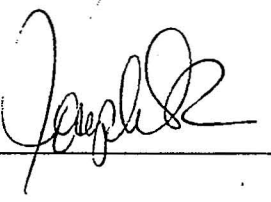
Joseph S. Sonk, Ph.D.
Assistant Vice President
Worldwide Regulatory Affairs

N020527
Prempro™/ Premphase®
Conjugated Estrogens / Medroxyprogesterone Acetate Tablets

Lower Dose of Prempro™ 0.3mg/1.5mg

Item 20: Pediatric Rule (Waiver Requested)

In accordance with 21 CFR §314.55, Wyeth-Ayerst believes that pediatric data is not required for inclusion within this application. This application is for the addition of a lower dose of previously approved Prempro™ /Premphase® products that are indicated for postmenopausal symptoms, i.e., treatment of vasomotor symptoms, treatment of vulvar and vaginal atrophy and the prevention of osteoporosis. This product is not indicated for any pediatric population.

Signature 

Joseph S. Sonk, Ph.D.
Assistant Vice President
Worldwide Regulatory Affairs

NDA 20-527

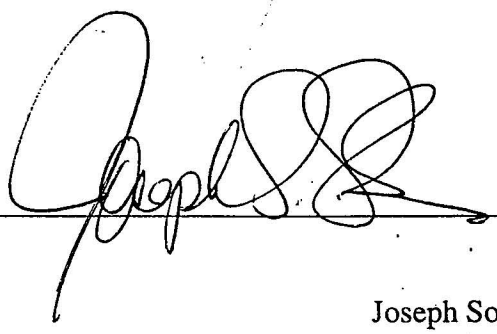
Prempro™ / Premphase®
Conjugated Estrogens and Medroxyprogesterone Acetate Combination Tablets

Lower Dose of Prempro™ 0.3/1.5

Indication
Vasomotor Symptoms
Vulvar and Vaginal Atrophy

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

The undersigned certifies that Wyeth-Ayerst did not and will not knowingly use in any capacity the services of any person debarred under subsection (a) or (b) [section 306 (a) or (b)] of the Generic Drug Enforcement Act of 1992 in connection with NDA 20-527 for Conjugated Estrogens and Medroxyprogesterone Acetate Combination Tablets.

Signature 

Joseph Sonk, Ph. D.
Assistant Vice President
Worldwide Regulatory Affairs

MEMORANDUM

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

Date: November 27, 2001

From: Jeanine Best, M.S.N., R.N.
Senior Regulatory Associate
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure Documents

To: NDA 20-527/SE1-024

I have reviewed the financial disclosure information submitted by Wyeth-Ayerst Laboratories in support of their SNDA 20-527/S-02.

One study was conducted to assess the safety and efficacy of Prempro/Premphase (conjugated estrogens/medroxyprogesterone acetate tablets) 0.3/1.5 mg Tablets for the treatment of vasomotor symptoms associated with menopause, and vulvar and vaginal atrophy.

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

The Financial Certification and Disclosure Information submitted November 5, 2001, was already submitted, reviewed and found acceptable for NDA 20-527/S-017. This SE1 comprises a re-filing of the CE/MPA 0.3/1.5 mg strength dose. This dose-strength was originally submitted to NDA 20-527/S-017, and withdrawn on April 3, 2001. Study 309-US was conducted to support all dose-strengths submitted to NDA 20-527/S-017.

Conclusion:
Per the January 29, 2001, Memo for Review of Financial Disclosure for NDA 20-527/S-017:

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

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

/s/

Jeanine Best
11/27/01 01:25:28 PM
CSO

20-527 / S-151

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

I 8 02 NDA 20

54

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	Premarin 0.3mg/MPA 1.5 mg	Study 309 - US
	(see attached lists)	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Joseph S. Camardo, MD ~~Mr. Robert Haller~~	Sr VP - Clinical R & D VP - R & D Finance
FIRM/ORGANIZATION	
Wyeth - Ayerst Research	
SIGNATURE	DATE
	September 6, 2001

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Created by: PSG Media Arts (301) 443-2454 EF

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Premarin 0.3 mg/MPA 1.5 mg
Study 309-US

The Clinical Investigators listed below include only those whose site enrolled patients in the above referenced study.

Last Name	First	MI
Ackerman	Gary	E
Alvarez	Benito	
Anthis	Cynthia	
Applewhite	Grace	C.
Archer	David	F.
Attia	George	
Ayers	Charletta	
Bachmann	Gloria	
Bagnell	Kelly	
Baker	Jay	M.
Baker	Robert	
Ballagh	Susan	A.
Baron	Mira	
Bass	Katherine	
Battistini	Michelle	
Bellin	Sandra	
Bello	Sandra	
Bergstrom	John	
Berlin	Michelle	
Blacker	Charla	
ardman	Lynn	Amy
ookman	Laura	
Bracero	Nabel	
Breitkopf	Lyle	
Bremner	Teresa	
Brodzinsky	Laura	
Brooks	G.	Gary
Bulow	Seth	
Burry	Kenneth	
Bush	Trudy	
Butler	William	
Calkins	John	
Campbell	Margie	
Carr	Bruce	R.
Carson	Linda	
Cedars	Marcelle	I.
Chang	Peter	
Chapman	Julie	Ann
Chen	Bertha	
Chen	Eileen	
Chen	M.	Dwight
Chesnut	Charles	H.
Chiang	Siene	
Cho	Michael	
Christian	Rose	
ristian	Jeffrey	S.
upp	Ernest	

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Premarin 0.3 mg/MPA 1.5 mg
Study 309-US

The Clinical Investigators listed below include only those whose site enrolled patients in the above referenced study.

Last Name	First	MI
Clisham	P.	Ron
Cockrell	Marion	
Cohen	Matthew	
Colie	Christine	
Confino	Edmond	
Cook	Christine	
Cooke	Robert	
Cosin	Jonathan	A.
Coulam	Christina	
Cowan	Bryan	D.
Creasman	William	T.
Creinin	Mitchell	
Cunningham	Jennifer	
Damario	Mark	
Daniels	Kay	
Davis	Ann	J.
Dawood	Yusoff	
Deal	Chad	
DeCherney	Alan	H.
Diamond	Michael	
[illegible]iem	Klaus	
[illegible]trich	Janet	
[illegible]nsay	Rosalyn	
Ditkoff	Edward	
Dominiquez	Celia	
Dorin	Maxine	
Downs	Levi	Stanford
Drosinos	Sophia	
Dumesic	Daniel	
Eblen	Abby	
Ebert	Gary	
Edraki	Tina	
Eisenberg	Esther	
Eisinger	Katarina	
El-Asfouri	Souhail	
Embrescia	James	M.
Emery	Danielle	
Emmons	Sandra	
English	Susan	C.
Estrin	Margaret	
Evans	Cynthia	
Evans	Judith	
Evans	Pamela	
Fang	Jane	
[illegible]allens	Thomas	
[illegible]scher	Robin	
[illegible]ssum	Gregory	

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Premarin 0.3 mg/MPA 1.5 mg
Study 309-US

The Clinical Investigators listed below include only those whose site enrolled patients in the above referenced study.

Last Name	First	MI
Fowler	Jeffrey	M.
Frankfurter	David	
Fylstra	Donald	
Gallagher	J.	Christopher
Garcia	Francisco	
George	Karen	
Ghosh	Kris	
Ginsburg	Kenneth	A.
Gleason	Brian	P.
Goldfarb	Alvin	
Goldfarb	James	
Gomez-Lobo	Veronica	
Good	Andrew	
Goodman-Gruen	Deborah	
Gorill	Marsha	Jan
Gorodeski	George	
Goudas	Vasilios	
Graczykowski	Jacek	
Graubert	Michael	
Griffin	Eric	
all	Lori-Linell	H.
npton	Harriette	L.
arms	Roger	
Harrington	J.	Timothy
Hecht	Bryan	
Heine	M.	Wayne
Herman	Robert	
Hershkind-DeSoto	Keri	
Herzog	Paul	
Hines	Randall	S.
Hoeger	Kathleen	
Holland	Laura	
Holley	Robert	L.
Homesley	Howard	
Huang	Jaou-Chen	
Hurd	William	W.
Hurst	Bradley	S.
Isaacs	John	D.
Jackson	Susan	
Jew	Edward	
Johnson	Peter	R.
Johnston	C.	Conrad
Jurema	Marcus	
Kalro	Brinda	
malamma	Meenakshia	
merer-Doak	Dorothy	
rounos	Garry	

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Premarin 0.3 mg/MPA 1.5 mg
Study 309-US

...ne Clinical Investigators listed below include only those whose site enrolled patients in the above referenced study.

Last Name	First	MI
Kazer	Ralph	
Kennedy	Joseph	
Kent	Howard	
Kessel	Bruce	
Kim	Moon	H.
Kipersztok	Simon	
Kiwi-	Robert	
Kleerekoper	Michael	
Klein	Steven	
Kolb	Bradford	
Kolp	Lisa	
Kowalczyk	Carole	
Krasnow	Joel	
Kubik	Carolyn	
Kutteh	William	
LaValleur	June	
Leach	Richard	E.
Lee	Harry	S.
Legino	Lonny	
Levine	Jeffrey	
...evitt	Robert	
...vis	Vivian	
...nden	Milton	
Lindsay	Robert	
Ling	Frank	W.
Lipscomb	Gary	
Lisbona	Hanna	
Liu	James	
Lobo	Rogerio	A.
London	Steve	N.
Lu	Peter	
Lukert	Barbara	
Lynch	Kelly	
Mandell	Elizabeth	
Manganiello	Paul	
Marcum	Ronald	
Maroulis	George	
Mayer	James	
McCracken	Tersh	
McGinnis	Kevin	
McLeod	Paul	
Meeks	G.	Rodney
Mehta	Zarna	
Mershon	John	
...indazitis	Nicholas	
...eiterlad	Magdy	
...ck	Lynette	

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Premarin 0.3 mg/MPA 1.5 mg
Study 309-US

The Clinical Investigators listed below include only those whose site enrolled patients in the above referenced study.

Last Name	First	MI
Moghissi	Kamran	S.
Montgomery-Rice	Valerie	
Morgan	Dorcas	
Moritz	Jacques	L.
Murray	Karuna	P.
Murray	Shona	
Muse	Kenneth	N.
Nagy	Annamarie	
Najmabadi	Sam	
Nani-Marchiori	Jane	
Natofsky	Jeryl	
Neale	Donna	
Neuwirth	Robert	S.
Odem	Randall	R.
Olson	Thomas	
Padilla	Luis	Alfonso
Paley	Pamela	(formerly Carney)
Palmgren	Muriel	
Parsons	Anna	K.
Patton	Phillip	
Penzias	Alan	S.
·ez	Raimel	
eskin	Barry	
Peskin	Julian	
Petranick	Kimberly	
Phillips	Nancy	A.
Pierson, Jr.	Richard	N.
Pinkerton	JoAnn	
Poindexter	Alfred	N.
Polan	Mary	Lake
Portera	Chris	
Portera	Greg	
Pryor	Joseph	A.
Puckett	Tony	
Purdon	Thomas	
Puscheck	Elizabeth	
Raines	Jeff	
Raisz	Lawrence	G.
Ramos	Manfred	
Ramsdell	Joe	W.
Ratts	Valerie	S.
Ravnikar	Veronica	A.
Rebar	Robert	W.
Reed	Bill	
·indollar	Richard	H.
·iter	Ruth	
·a	Matthew	

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Premarin 0.3 mg/MPA 1.5 mg
Study 309-US

The Clinical Investigators listed below include only those whose site enrolled patients in the above referenced study.

Last Name	First	MI
Rhoton-Vlasak	Alice	
Richard-Davis	Gloria	
Richter	Holly	
Rivlin	Michael	
Rizk	Botros	
Robinette	Lynda	
Rogers	Rebecca	
Rogers	Nickola	
Roy	Tracey	
Samet	Jonathan	
Santos	Lisette	
Sartor	Sissy	
Scheiber	Michael	A.
Schlaff	William	
Schneider	Diane	
Schwartz	Maurice	
Scialli	Anthony	
Session	Donna	
Shepard	Marguerite	
Shipul	Arthur	
houkri	Kamal	
oupe	Donna	
imon	James	A.
Singh	Gita	
Singh	Anita	
Sinofsky	Francine	
Skaggs	Kate	
Smith	Joanne	
Smith	Kevin	
Sohn	Sae	
Speroff	Leon	
Stelling	James	R.
Stovall	Thomas	G.
Summitt, Jr.	Robert	L.
Taylor	Margaret	
Tazuke	Salli	
Telles	Tracy	
Thomas	Grace	
Thomas	Michael	A.
Thorneycroft	Ian	
Thorton	Kim	
Thornton	Melvin	
Tobin	Jordan	
Trout	Wayne	C.
ai	Charles	
eddel	George	
iggs	Leo	

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 1

Premarin 0.3 mg/MPA 1.5 mg
Study 309-US

The Clinical Investigators listed below include only those whose site enrolled patients in the above referenced study.

Last Name	First	MI
Uhler	Meike	L.
Underwood	Paul	B.
Utian	Wulf	H.
Vadlamani	Indira	
Valle	Rafael	
Varner	R.	Edward
Varner	Steve	
Veloudis	George	
Vexler	David	
Viyouh	Nicholas	
Vlahos	Nikos	
Vogt	Val	
Walsh	Brian	
Wang	Chun-Yeh	
Warburton	Keeling	A.
Warren	Michelle	
Watanabe	Margaret	R.
Wei	Albert	K.
Weinstein	Louis	
Weiss	Bernard	
helan III	Joseph	G.
ese	Deborah	
ilcox	John	
Wild	Robert	A.
Williams	Daniel	
Williams	Stan	
Williams	Sterling	
Winkel	Craig	A.
Word	Larry	
Wylen	Michele	
Yeko	Timothy	R.
Yussman	Marvin	A.
Zacur	Howard	
Zinaman	Michael	
Zoma	Willie	
Zuckerman	Andrea	L.
Zuniga	Manuela	

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators
Attachment to Section 3

Premarin - 0.3 mg/MPA 1.5 mg
Study 309-US

Letters requesting Financial Disclosure were sent to the Clinical Investigators listed below as their site enrolled patients in the above referenced study. If no reponse was received from the initial request, additional attempts were performed (such as mail, phone, fax, e-mail) in order to meet the Financial Disclosure requirement. See comments below for explanation as to why Financial Disclosure forms could not be obtained.

Last Name	First	MI	Comments
(b) (6)			

FDA Form 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators

Premarin - 0.3 mg/MPA 1.5 mg
Study 309-US

The following individuals were listed on 1572's however, Financial Disclosure Forms were not received because they either did not participate in the study or the level of their involvement does not require the submission of Financial Disclosure Forms.

Last Name	First	MI	Comments
(b) (6)			

PREMARIN .3 MG/MPA 1.5 MG SUBMISSION

Amount Paid 2/99 thru 7/01

Investigator Name	Study #	Visiting Professors	CME	Honoraria/Travel	Consultant Meeting	**Total**
(b) (6)						

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning (b) (6), who participated as a clinical investigator in the submitted study Premarin 0.3 mg/MPA 1.5 mg, Study 309 - US, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Name of clinical investigator — *Name of clinical study*

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Joseph S. Camardo, M.D. Mr. Robert Haller	Semior Vice President - Clinical R & D Vice President - R & D Finance
FIRM/ORGANIZATION Wyeth-Ayerst Research	
SIGNATURE	DATE September 6, 2001

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

Created by Electronic Document Services-USDHHS: (301)

Attachment
FDA Form 3455 - Disclosure: Financial Interests and Arrangements of Clinical Investigators

(b) (6)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning (b) (6) *Name of clinical investigator*, who participated as a clinical investigator in the submitted study Premarin 0.3 mg/MPA 1.5 mg *Name of* Study 309 - US *clinical study*, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Joseph S. Camardo, M.D. Mr. Robert Haller	Sernior Vice President - Clinical R & D Vice President - R & D Finance
FIRM/ORGANIZATION Wyeth-Ayerst Research	
SIGNATURE	DATE September 6, 2001

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

Attachment
FDA Form 3455 - Disclosure: Financial Interests and Arrangements of Clinical Investigators

(b) (6)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning (b) (6) (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study Premarin 0.3 mg/MPA 1.5 mg (*Name of clinical study*), is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

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Joseph S. Camardo, M.D. Mr. Robert Haller	Sernior Vice President - Clinical R & D Vice President - R & D Finance
FIRM/ORGANIZATION Wyeth-Ayerst Research	
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Created by Electronic Document Services/USDHHS: (301) EF

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FIRM/ORGANIZATION Wyeth-Ayerst Research	
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FIRM/ORGANIZATION Wyeth-Ayerst Research	
SIGNATURE	DATE September 6, 2001

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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Form Approved: OMB No. 0910-0396
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Name of clinical investigator

Name of clinical study

Please mark the applicable checkboxes.

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NAME	TITLE
Joseph S. Camardo, M.D. Mr. Robert Haller	Senior Vice President - Clinical R & D Vice President - R & D Finance
FIRM/ORGANIZATION Wyeth-Ayerst Research	
SIGNATURE	DATE
	November 1, 2001

Paperwork Reduction Act Statement

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5600 Fishers Lane, Room 14-72
Rockville, MD 20857

Created by Electronic Document Services-USDHHS: (301) EF

Attachment
FDA Form 3455 - Disclosure: Financial Interests and Arrangements of Clinical Investigators

(b) (6)

[redacted]

MEMORANDUM

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

Date: January 29, 2001

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

Subject: Review of Financial Disclosure documents

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

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

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

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

Documents Reviewed:

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

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

1. Regarding the July 19, 2000 facsimile:
   a) The number of patients enrolled per subinvestigator is actually per site. For example, a total of (b) (6) patients were seen at Site (b) (6), which had six non-compliant subinvestigators, not (b) (6) patients per subinvestigator.
   b) The number of patients at Site (b) (6)
   c) The number of patients analyzed was 2,673. The term "analyzed" is equivalent to the terms "active" and "completed" used in individual financial disclosure statements.

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

2. Regarding the October 17, 2000 submission
   a) (b) (4) was added as a (sub)investigator in an August 30, 2000, submission, which is why (b) (6) name did not appear on the initial certification dated March 17, 2000.

Study 309-US

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

- (b) (6)

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

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

Conclusion:

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

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

Telefax Number: (610) 964-5973

DATE: *July 19, 2000*

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

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

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

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

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

Lana,

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

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

Regards,

JoAnne M. Bissinger
Manager, Worldwide Regulatory Affairs

DRUDP.fax

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

Investigator	Site # (Principe Investigator)	No. of Patient
(b) (6)		

2,673 patients were analyzed

/s/

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

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 6, 2002

TIME: 1:00 p.m.

LOCATION: PKLN 17B-43

APPLICATION: NDA 20-527/S-024

TYPE OF MEETING: 9-month status/labeling meeting

MEETING CHAIR: Theresa van der Vlugt, M.D.

MEETING RECORDER: Dornette Spell-LeSane, NP-C

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1. Theresa van der Vlugt, M.D.	Acting Medical Team Leader	Division of Reproductive and Urologic Drug Products, DRUDP(HFD-580)
2. Dornette Spell-LeSane, NP-C	Regulatory Project manager	DRUDP HFD-580

BACKGROUND:
The Supplemental application was submitted on November 5, 2001, received November 7, 2001. The supplement proposes the new 0.03 mg CE/1.5 mg MPA dose for the treatment of moderate to severe vasomotor symptoms associated with the menopause and the treatment of vulvar and vaginal atrophy. The User Fee goal date is September 7, 2002. An approvable action was taken for NDA 20-527/S026 by DRUDP and for NDA 21-396 by the Division of Metabolism and Endocrine Drug Products on July 25, 2002, for the prevention of postmenopausal osteoporosis for the same Prempro doses.

MEETING OBJECTIVES:
To review labeling comments for this Supplement 024 incorporating labeling comments from supplement 026, and NDA 21-396 as well as, the proposed CBE changes from the sponsor as a result of the recent Women's Health Initiative (WHI) findings.

DISCUSSION POINTS:

- See attached labeling; additions are indicated by double underline and deletions are indicated by ~~strike through~~, comments are in **14 font bold**.

ACTION ITEMS:

- PM to prepare AP for review

Minutes Preparer: _____
Dornette Spell-LeSane, Project Manager

Chair Concurrence: _____
Theresa van der Vlugt, Acting Medical Team Leader

cc: Original
HFD-580/ 20-527/Div. Files
HFD-580/Slaughter, van der Vlugt,Lin,Jarugula,NG

Drafted by: SPELL-LESANE, 8.14.02
Initialed by: van der Vlugt, 8.16.02
final: Spell-LeSane, 8.21.02
MEETING MINUTES

61 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

___X___ Draft Labeling (b4)

___X___ Draft Labeling (b5)

_____ Deliberative Process (b5)

_____ Law Enforcement Action (b7)

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

/s/

Theresa Van Der Vlugt
8/21/02 10:20:48 AM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 2, 2002

TIME: 10:30 a.m.

LOCATION: PKLN 17B-43

APPLICATION: NDA 20-527/S-024

TYPE OF MEETING: 8-month status meeting

MEETING CHAIR: Theresa van der Vlugt, M.D.

MEETING RECORDER: Dornette Spell-LeSane, NP-C

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1. Theresa van der Vlugt, M.D.	Acting Medical Team Leader	Division of Reproductive and Urologic Drug Products, DRUDP(HFD-580)
2.David Lin, Ph.D.	Chemistry Team Leader	Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
3.Dornette Spell-LeSane, NP-C	Regulatory Project Manager	DRUDP HFD 580

BACKGROUND:
The Supplemental application was submitted on November 5, 2001, received November 7, 2001. The User Fee goal date is September 7, 2002. The sponsor submitted a supplemental NDA (NDA 21-396) for the same Prempro doses to the Division of Metabolism and Endocrine Drug Products for the prevention of postmenopausal osteoporosis. The User Fee goal date for that supplemental application is July 25, 2002.

MEETING OBJECTIVES: To discuss the status of Supplement 24 that proposes the new 0.03 mg CE/1.5 mg MPA dose for the treatment of moderate to severe vasomotor symptoms associated with the menopause and the treatment of vulvar and vaginal atrophy.

DISCUSSION POINTS:

Chemistry:
- chemistry review is completed
- the manufacturing site inspections are still pending

Biometrics:
- the review is complete

Clinical Pharmacology:
- a draft review has been submitted to the Team Leader

Clinical:
- a draft review has been submitted to the Team Leader

Labeling:
- clinical labeling comments are posted on the N drive

ACTION ITEMS:
- labeling meeting in one month

Minutes Preparer: _____
Dornette Spell-LeSane, Project Manager

Chair Concurrence: _____
Theresa van der Vlugt, Acting Medical Team Leader

cc: Original
HFD-580/ 20-527/Div. Files
HFD-580/Slaughter, van der Vlugt,Lin,Jarugula,NG

Drafted by: SPELL-LESANE, 8.14.02
Initialed by: van der Vlugt, Lin, 8.15.02
final: Spell-LeSane, 8.21.02
MEETING MINUTES

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

/s/

Theresa Van Der Vlugt
8/21/02 10:16:44 AM

0527

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

ORIGINAL

Worldwide Regulatory Affairs

RECEIVED
JUL 10 2002
CDR/CDER

NDA SUPPL AMENDMENT

July 8, 2002

Sel-034-BM

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

Daniel Shames, MD, 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

RECEIVED
JUL 11 2002
HFD-580/CDER

Dear Dr. Shames:

Reference is made to NDA No. 20-527/S-024 for Prempro (conjugated estrogens / medroxyprogesterone acetate tablets), Premphase (conjugated estrogens / medroxyprogesterone acetate tablets) submitted to DRUDP on November 5, 2001.

Further reference is made to a request via facsimile from Ms. Dornette Spell-Lesane on June 4, 2002 for lipid profile datasets for patients in the 2-year metabolic substudy of 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* and SAS program used to generate the data. The purpose of this submission is to provide the following files, in accordance with FDA guidance, *Providing Regulatory Submissions in Electronic Format – NDAs*, and thereby amend Item 11 of NDA No. 20-527/S-024:

1. cover.pdf (Cover letter with attachments):
   - Lipid data (Analysis result for lipid data, Intent to Treat (ITT) population)
   - LDL/HDL ratio data (Analysis result for LDL/HDL ratio data, ITT population)
2. lipid.xpt (SAS transport file for the 12 lipid parameters),
3. lipratio.xpt (SAS transport file for LDL/HDL ratio)
4. define.pdf (Table of contents listing lipid and lipratio datasets; Description files for lipid.xpt, lipratio.xpt)

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

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

Wyeth

FACSIMILE

Date: 6/12/02

Number of pages (including cover): 2

To: Ms. Dornette Spell Lasane

From: Jennifer D. Norman JDN

Telephone: 301 827 4260

Department: Worldwide Regulatory Affairs

Fax: 301 827 4267

Telephone: 484 865 3749

cc:

Fax: 484 865 9214

Urgent ☒ For your review ☐ ☐ Please reply asap ☐ Please comment

Remarks:

Dear Ms. Lasane:

RE: NDA 20-527/S-024

In reference to my voice mail to you today regarding the Division's request for lipid profiles for year 2 substudy patients of Protocol 0713D2 – 309- US, please find attached the Table entitled Summary Tabulation of Lipids. We are aware that this table only contains Total Cholesterol; however, we would appreciate your confirming that this is the type/format of information, for which the reviewer is requesting. If this is the type/format of information that the reviewer is seeking, then we will arrange to have the complete lipid profiles displayed for year 2 substudy.

Thank you
Jennifer D. Norman

002
WYETH REG. AFFAIRS
06/12/02 WED 13:24 FAX 484 865 9214

Table LIP.1 : Summary Tabulation of Lipids
Percent Change from Baseline, Comparison Within and Between Groups

Treatment Group	Timeslot	No. of Pairs	Baseline Mean	Baseline SD	Observed Mean	Observed SD	% Change from B/L Adjusted Mean	% Change from B/L SE	P-Values Within Group	P-Values Versus Placebo	P-Values Versus Premarin
TOTAL CHOLESTEROL (mmol/L)											
Group F 0.3	CYCLE 6	80	5.72	0.89	5.80	1.12	1.44	1.15	0.19	0.95	
	CYCLE 13	75	5.67	0.87	5.76	0.91	1.74	1.22	0.11	0.40	
	CYCLE 19	65	5.73	0.82	5.85	0.85	1.65	1.34	0.066	0.40	
	CYCLE 26	60	5.77	0.81	5.90	0.90	2.24	1.45	0.073	0.086	
Group G 0.3/1.5	CYCLE 6	89	5.47	0.90	5.42	0.99	-0.44	1.08	0.65	0.24	0.23
	CYCLE 13	81	5.41	0.87	5.50	1.01	1.59	1.16	0.14	0.35	0.93
	CYCLE 19	75	5.41	0.88	5.39	0.94	-0.22	1.24	0.88	0.057	0.30
	CYCLE 26	74	5.39	0.86	5.53	0.86	2.90	1.31	0.015	0.15	0.73
Group H Placebo	CYCLE 6	84	5.56	0.90	5.60	0.89	1.34	1.12	0.23		
	CYCLE 13	78	5.51	0.88	5.66	0.93	3.13	1.19	0.006		
	CYCLE 19	63	5.53	0.89	5.71	0.95	3.21	1.34	0.005		
	CYCLE 26	60	5.51	0.90	5.81	1.01	5.68	1.44	<0.001		

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 870)** **Tracking/Action Sheet for Formal/Informal Consults**

From: Venkateswar Jarugula, Ph.D., HFD-870			To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission	
DATE: 6/5/02	IND No.:	NDA No. 20527 S-024	DATE OF DOCUMENT 11/07/01	
NAME OF DRUG Prempro/Premphase	PRIORITY CONSIDERATION		Date of informal/Formal Consult:	

NAME OF THE SPONSOR: Wyeth Ayerst

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☒ OTHER *(SPECIFY BELOW)* *Efficacy Supplement*
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated) ☐ E-mail comments to: ☐Medical ☐Chemist ☐Pharm-Tox ☐Micro ☐Pharmacometrics ☐Others (Check as appropriate and attach e-mail)	☐ Oral communication with Name: [ ] ☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ Formal Review/Memo (attached) ☒ See comments below ☐ See submission cover letter ☐ OTHER *(SPECIFY BELOW)*: [ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

NDA 20-527/S-024 is an efficacy supplement for 0.3 mg CE (conjugated estrogens)/1.5 mg MPA (medroxyprogesterone acetate) tablets. The current supplement includes two relative bioavailability studies (0713D2-119-US and 0713D2-120-US) which have been also submitted in NDA20-527/SLR-017. The Clinical Pharmacology and Biopharmaceutics review of NDA 20-527/SLR-017 by Dr. Johnny Lau concluded that the pharmacokinetic data for Prempro/Premphase tablets including the proposed dose in the current supplement are acceptable (please refer to the attached review). Therefore, there is no additional pharmacokinetic data/information in the current supplement for review.

The phase IV commitment to develop appropriate in vitro dissolution method for MPA as stated in Dr. Johnny Lau's review (see attached review) should be communicated to the sponsor in the approval letter for this supplement.

SIGNATURE OF REVIEWER: _____	Date _____
SIGNATURE OF TEAM LEADER: _____	Date _____

CC.: HFD # [870]; TL: [Parekh]; DD: [Malinowski]; PM:

Screening of New NDAs
Division of Biometrics II

NDA #: 20-527/S-024

Trade Name: Prempro™ (Conjugated Estrogens/Medroxyprogesterone Aetate Tablets)
Premphase® (Conjugated Estrogens/Medroxyprogesterone Acetate Tablets)

Sponsor: Wyeth-Ayerst Laboratories

Indication: Treatment of moderate to severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy

User Fee Goal Date: September 7, 2002

Date of Submission: November 5, 2001

Date of 45 Day Meeting: December 19, 2001

Medical Reviewer : Therasa van der Vlugt, M.D. (HFD-580)

Project Manager: Diane Moore (HFD-580)

Screened by: Moh-Jee Ng , M.S. (HFD-715)

Comments: Data and analysis are included in this submission, this is fileable

CHECKLIST

Item	Check (NA if not applicable)
Index sufficient to locate necessary, tables, etc.	Yes
Original protocols & subsequent amendments available in the NDA	Yes
Designs utilized appropriate for the indications requested	Yes
Endpoints and methods of analysis spelled out in the protocols	Yes
Interim analyses (If present) planned in the protocol and appropriate adjustments in significance level made	NA
Appropriate references included for novel statistical methodology (if present)	NA
Sufficient date listings and intermediate analysis tables to permit a statistical review	Yes
Data from primary studies on diskettes and/or Electronic submitted	Yes
Intent-to-treat analyses	Yes
Effects of dropouts on primary analyses investigated	Yes
Safety and efficacy for gender, racial, and geriatric subgroups investigated	NA

Brief Summary of Controlled Trials

Study Number	Study Design	Treatment Group	Sample Size	Duration of Treatment
0713D2-309-US	Interim 1-year prospective, Double-blind, randomized, multicenter, Phase 3 study of multiple doses of conjugated estrogens and conjugated estrogens plus medroxyprogesterone acetate in postmenopausal women	A: 0.625 mg CE	348	1 year
		B: 0.625 mg CE / 2.5 mg MPA	331	
		C: 0.45 mg CE	338	
		D: 0.45 mg CE / 2.5 mg MPA	340	
		E: 0.45 mg CE / 1.5 mg MPA	331	
		F: 0.3 mg CE	326	
		G: 0.3 mg CE/1.5 mg MPA	327	
		H: Placebo	332	

Moh-Jee Ng, M.S.
Mathematical Statistician

Concur: Mike Welch, Ph.D.

cc. NDA 20-527/S-017
HFD-580 / Division file
HFD-580 / TvanderVlugt, DMoore, SSlaughter, DShames
HFD-715/ENevius, MWelch, CAnello, MNg,

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

/s/

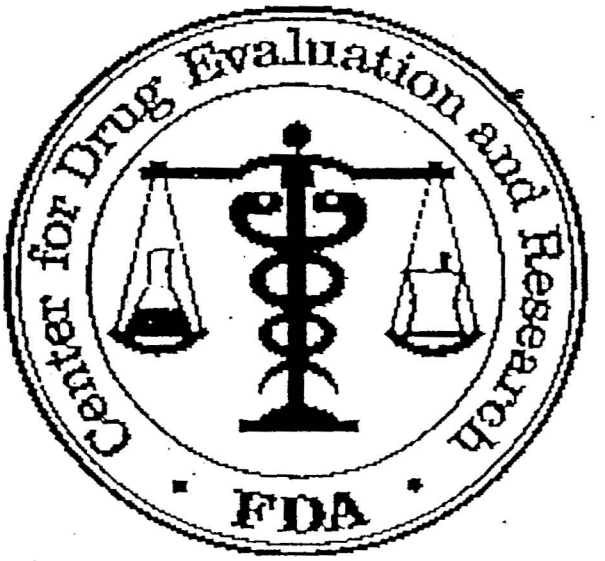
Moh-Jee Ng
12/19/01 03:21:34 PM
BIOMETRICS

Mike Welch
12/21/01 08:39:50 AM
BIOMETRICS

2 pages

D AND DRUG ADMINISTRATION
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
DOCUMENT CONTROL ROOM 17B-20
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: 6/4/02



TO:

Name: Jennifer Norman

Fax No: 484-865-9214

Phone No:

Location:

FROM:

Name: Doenette Spell-LeSane

Fax No: (301) 827-4267

Phone No: (301) 827-4260

Location: FDA, Division of Reproductive and Urologic Drug Products

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above the above address by mail. Thank you.

Comments: Row 6 in table to Change HDL-C/LDL-C

concurrence:

Table 1
Mean Percent Change from Baseline of Lipid Profile
ITT population

		Prempro 0.3mg CE/1.5 mg MPA			Premarin 0.3 mg CE			Placebo			P-values		
	Time Period	N	Mean (SD)	Mean Percent Change from baseline	N	Mean (SD)	Mean Percent Change from baseline	N	Mean (SD)	Mean Percent Change from baseline	Within group	Versus Placebo	Versus Premarin
Total -C	Baseline Cylce 6 Cycle 13 Cycle 19 Cycle 26												
HDL-C	Baseline Cylce 6 Cycle 13 Cycle 19 Cycle 26												
HDL_2-C	Baseline Cylce 6 Cycle 13 Cycle 19 Cycle 26												
LDL-C	Baseline Cylce 6 Cycle 13 Cycle 19 Cycle 26												
VLDL-C	Baseline Cylce 6 Cycle 13 Cycle 19 Cycle 26												
LDL-C /HDL-C	Baseline Cylce 6 Cycle 13 Cycle 19 Cycle 26												
Triglycerides	Baseline Cylce 6 Cycle 13 Cycle 19 Cycle 26												

OD AND DRUG ADMINISTRATION
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
DOCUMENT CONTROL ROOM 17B-20
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: 5/31/02

TO:

me: Jennifer Norman

Fax No: 484-865-9214

Phone No:

Location:

FROM:

Name: Dornette Spell-LeSane

Fax No: (301) 827-4267

Phone No: (301) 827-~~4260~~ 7514

Location: FDA, Division of Reproductive and Urologic Drug Products

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Comments:

Please create the attached table. Provide data sets and SAS program used to generate the table

concurrence:

Re: NDA 20-527 / S017, S024

NDA 20-527/S-017 Prempro/Premphase

Please provide the datasets of Protocol 0713D2-309-US, SAS programs used to generate the table as below.

Mean Percent Change from Baseline of Lipid Profile
ITT population

		Prempro 0.3mg CE/1.5 mg MPA			Premarin 0.3 mg CE			Placebo			P-values		
	Time Period	N	Mean (SD)	Mean Percent Change from baseline	N	Mean (SD)	Mean Percent Change from baseline	N	Mean (SD)	Mean Percent Change from baseline	Within group	Versus Placebo	Versus Premarin
Total -C	Baseline Cylce 6 Cycle 13 Cycle 19 Cycle 26												
HDL-C	Baseline Cylce 6 Cycle 13 Cycle 19 Cycle 26												
HDL_2-C	Baseline Cylce 6 Cycle 13 Cycle 19 Cycle 26												
LDL-C	Baseline Cylce 6 Cycle 13 Cycle 19 Cycle 26												
VLDL-C	Baseline Cylce 6 Cycle 13 Cycle 19 Cycle 26												
HDL-C /LDL-C	Baseline Cylce 6 Cycle 13 Cycle 19 Cycle 26												
Triglycerides	Baseline Cylce 6 Cycle 13 Cycle 19 Cycle 26												

D AND DRUG ADMINISTRATION
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
DOCUMENT CONTROL ROOM 17B-20
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: 5/31/02

TO:

Name: Jennifer Norman

Fax No: 494-865-9214

Phone No:

Location:

FROM:

Name: Doenette Spell-LaSane

Fax No: (301) 827-4267

Phone No: (301) 827-4260

Location: FDA, Division of Reproductive and Urologic Drug Products

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Comments:

concurrence:

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
FAX-MEMO

Date: May 31, 2002

From: Dornette Spell-LeSane, NP-C, MHA
Regulatory Project Manager (HFD-580)

To: Jennifer Norman, R.Ph.
Associate Director, Wyeth-Ayerst

Re: NDA 20-527/S-024
Request for Information

Regarding the substudy data submitted in Supplement 24 and the number of cases of hyperplasia diagnosed only in year-2 in the substudy subjects. Table 9.4.2.2.3B provides the total number of hyperplasia diagnosed at cycle 13 in the substudy group while Table 9.4.2.2.3A provides the total cases of hyperplasia at cycle 26. Please confirm that the total cases at cycle 26 include the cases reported at cycle13.

REQUESTS FOR 0.3 Mg Prempro/Premphase ®
NDA 20-527

Please provide the following variabales of dataset Study 309 as SAS files or ASCII on diskette:

Patient Id
Protocol No. (0713D2-309-US)
Investigator ID
Age (in years)
Treatment (e.g. A: 0.625 mg, …, H: Placebo)
Date of randomization
Date of discontinuation from study
Primary reason for discontinuation from study
Study Duration (day)
Completed study? (Yes/No)
Which Cycle patient has hyperplasia diagnosis?
Hyperplasia Patient (Yes/No)
Biopsy Performed? (Yes/No)
Date of Biopsy
Biopsy results

requested 2/11/02 DH

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 4, 2002

TIME: 1:00 p.m.

LOCATION: PKLN 17B-43

APPLICATION: NDA 20-527/S-024

TYPE OF MEETING: 7-month status meeting

MEETING CHAIR: Shelley Slaughter, M.D., Ph.D.

MEETING RECORDER: Dornette Spell-LeSane, NP-C

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1.Shelley Slaughter, M.D., Ph.D.	Medical Team Leader	Division of Reproductive and Urologic Drug Products, DRUDP(HFD-580)
3.David Lin, Ph.D.	Chemistry Team Leader	Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
4.Moh-Jee NG, M.S.	Biometrics Reviewer	DRUDP HFD-580
5.Theresa van der Vlugt, M.D.	Medical Officer	DRUDP HFD 580
6.Dornette Spell-LeSane, NP-C	Regulatory Project Manger	DRUDP HFD 580

BACKGROUND:
The Supplemental application was submitted on November 5, 2001, received November 7, 2001. The User Fee goal date is September 7, 2002. The sponsor submitted a supplemental NDA (NDA 21-396) for the same Prempro doses to the Division of Metabolism and Endocrine Drug Products for the prevention of postmenopausal osteoporosis. The User Fee goal date for that supplemental application is July 25, 2002.

MEETING OBJECTIVES: To discuss the status of Supplement 24 that proposes the new 0.03 mg CE/1.5 mg MPA dose for the treatment of moderate to severe vasomotor symptoms associated with the menopause and the treatment of vulvar and vaginal atrophy.

DISCUSSION POINTS:

Chemistry:
- chemistry review is completed
- the manufacturing site inspections are ongoing
- approval status is based on results of the inspections

Biometrics:
- the review is ongoing
- information request sent and received from the sponsor and is under review

Clinical Pharmacology and Biopharmaceutics:
- the review is completed

Clinical:
- the review is ongoing

Labeling:
- a labeling supplement, 026 has been received from the sponsor and will be reviewed in conjunction with NDA 21-396; a separate action will be taken for S/024 on the September goal date
- S/024 label is on the N-drive for review

ACTION ITEMS:
- Next status meeting in one month

Minutes Preparer: _____
Dornette Spell-LeSane, Project Manager

Chair Concurrence: _____
Shelley Slaughter, Medical Team Leader

cc: Original
HFD-580/ 20-527/Div. Files
HFD-580/Slaughter, van der Vlugt,Lin,Jarugula,NG

Drafted by: SPELL-LESANE, 8.14.02
Initialed by: van der Vlugt, Lin, 8.16.02/NG, 8.19.02
final: Spell-LeSane, 8.21.02
MEETING MINUTES

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

/s/

Shelley Slaughter
8/21/02 01:43:22 PM
I concur.

WYETH-AYERST RESEARCH

OX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

LDWIDE REGULATORY AFFAIRS

ORIGINAL

CONTAINS TRADE SECRETS AND CONFIDENTIAL COMMERCIAL INFORMATION
PROTECTED FROM DISCLOSURE UNDER 5 U.S.C. §552(B)(4) AND 21 C.F.R. §20.61

NDA SUPP AMEND

April 29, 2002

RECEIVED

APR 30 2002

HFD-580/CDER

NDA 20-527/S-024
Prempro ™ (conjugated estrogens/medroxyprogesterone acetate tablets)
Premphase® (conjugated estrogens/medroxyprogesterone acetate tablets)

Daniel Shames, MD, 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

NDA SUPP AMEND

SE1-024-SU

See medical officer Review of S-024 J.J. van der Vlugt 5/13/02

Dear Dr. Shames:

Reference is made to NDA 20-527/S-024 submitted to the Division of Reproductive and Urologic Drug Products on November 5, 2001. Further reference is made to the 4-Month Safety Update submitted to DRUDP on March 5, 2002.

The purpose of this submission is to amend NDA 20-527/S-024 with regards to the 4-Month Safety Update. An error was noted on page 5 of the 4-Month Safety Update, Safety Surveillance Reports, Table 2 IND Safety Reports, concerning the dosage group for Patient No. 30914-0055 of Protocol 0713D2-309-US. Patient No. 30914-0055 received conjugated estrogens / medroxyprogesterone acetate tablets 0.45 mg/1.5 mg, not conjugated estrogens tablets 0.45 mg as noted in Table 2 submitted with the 4-Month Safety Update on March 5, 2002. As agreed to with Ms. Diane Moore on March 18, 2002, a replacement page 5 with the corrected dosage group for Patient No. 30914-0055 is provided with this submission.

If you have any questions regarding this submission, please contact the undersigned at (484) 865-3749.

9214

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Sincerely,

WYETH LABORATORIES

Jennifer D. Norman

Jennifer D. Norman, RPh
Associate Director,
Worldwide Regulatory Affairs

WYETH-AYERST RESEARCH

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

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 8 2002
HFD-580

March 7, 2002

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

SE1 024 (B5

NDA SUPPLEMENT
NDA SUPPLEMENT

Daniel Shames, MD, 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

Dear Dr. Shames:

Reference is made to NDA No. 20-527/S-024 for Prempro (conjugated estrogens / medroxyprogesterone acetate tablets), Premphase (conjugated estrogens / medroxyprogesterone acetate tablets) submitted to DRUDP on November 5, 2001.

The purpose of this submission is to amend NDA No. 20-527/S-024 in response to a request from DRUDP on February 11, 2002.

On February 11, 2002, Ms. Diane Moore, Project Manager, DRUDP, requested that the following variables from the datasets from Protocol 0713D2-309-US be combined into one file for the statistician reviewing the application:

Patient ID
Protocol 0713D2-309-US
Investigator ID
Age (yr.)
Treatment Group (A....H)
Date of Randomization
Date of Discontinuation from Study
Primary Reason for Discontinuation
Study Duration (day)
Completed Study (Y/N?)
Cycle patient has hyperplasia diagnosis
Hyperplasia (Y/N?)
Biopsy Performed (Y/N?)
Date of Biopsy
Biopsy Results

On February 13, 2002, Wyeth suggested that instead of providing a new file, we would provide a SAS program, which the reviewer would use to create the new file, and thereby make it easier for the reviewer to work with the data. Ms. Moore had confirmed that this would be acceptable.

Enclosed on one (1) CD-ROM are four (4) files, including a SAS program, designed to allow the statistician reviewing the application to combine the desired variables onto one file. The four (4) files included on this CD-ROM are as follows:

1. R61EBNEW.SAS - The SAS program
   This will allow variables from datasets to be combined into one file. Comments are included with this file to explain the program.

2. R61EBNEW.LOG - Log File
   The log file is created when the SAS program is run for verification that the program has been run correctly.

3. R61EBNEW.LIS – Output
   This file is created when the SAS program is run and allows for verification that the program has been run correctly. It contains the contents of the SAS file and four tabulations and one listing of data that matches the results in the General Medical Report (GMR) 38605.

4. R31NEW.XPT
   This is a new version of discontinuation data to be used with the SAS program in response to the variables requested.

This amendment is provided as electronic files. The approximate size of the submission is 316 MB 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,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman, RPh
Associate Director,
Worldwide Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIGINAL

WYETH-AYERST RESEARCH

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

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

RECEIVED
MAR 0 6 2002
CDR/CDER

March 5, 2002

NDA 20-527/S-024
Prempro ™ (conjugated estrogens/medroxyprogesterone acetate tablets)
Premphase® (conjugated estrogens/medroxyprogesterone acetate tablets)

Daniel Shames, MD, 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

SE1024(SU)

NDA SUPP AMEND

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 0 7 2002
HFD-580

Dear Dr. Shames:

Reference is made to NDA 20-527/S-024 submitted to the Division of Reproductive and Urologic Drug Products on November 5, 2001. This sNDA supports the use of low dose conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) tablets (CE 0.3 mg/MPA 1.5mg) for the treatment of moderate to severe vasomotor symptoms, and vulvar and vaginal atrophy.

The purpose of this submission is to provide the 4-Month Safety Update for the above referenced sNDA. This submission contains Item 9, 4-Month Safety Update for 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*, and Protocol 0713D2-312-JA, *A Double-Blind Clinical Study Comparing WJ-713/MPA and Estriol in the Treatment of Postmenopausal Osteoporosis*, which were included in NDA 20-527/S-024.

The 4-Month Safety Update is provided as an electronic file. The approximate size of the submission is 6.5 megabytes and is contained on one (1) CD-ROM. All files were scanned for viruses using McAfee VirusScan, version 4.03a, 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 submission, please contact the undersigned at (484) 865-3749.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman, RPh
Associate Director,
Worldwide Regulatory Affairs

TH-1019

WYETH-AYERST RESEARCH

PO BOX 8299 • PHILADELPHIA, PA 19101-8299

WORLDWIDE REGULATORY AFFAIRS

Division of American Home Products Corporation

CENTER FOR DRUG
RECD
JAN 28 2002
HFD-580
EVALUATION AND RESEARCH

ORIGINAL

SUPPL NEW CORRESP

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

021-024-C

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.

REVIEWS COMPLETED
CSO ACTION:
LETTER
DATE

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)

Filing Memorandum
Division of Reproductive and Urologic Drug Products

---

sNDA 20-527/S-024

Trade Name:	**Prempro™ (0.3 mg CE/1.5 mg MPA)**
Generic Name:	**Conjugated estrogens (CE)** **Medroxyprogesterone acetate (MPA)**
Sponsor:	**Wyeth-Ayerst Research** **P.O. Box 8299** **Philadelphia, PA 19101-8299**
Submission Date:	**November 5, 2001**
Date Received:	**November 7, 2001**
Indications:	**• Treatment of moderate to severe vasomotor symptoms associated with the menopause.** **• Treatment of vulvar and vaginal atrophy.**
Dose form:	**Tablet**
Treatment Schedule:	**Continuous for 28 days**
Dosage Regimen:	**0.30 mg CE plus 1.5 mg MPA**
User Fee Goal Date:	**September 6, 2002**
Filing Date:	**December 19, 2001**
Medical Reviewer:	**Theresa H. van der Vlugt, M.D., M.P.H.**

Submission Resume

This is a resubmission of the 0.3 mg CE/1.5 mg MPA dosage strength for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause.

On June 15, 2000, Wyeth-Ayerst submitted sNDA 20-527/S-017. Supplement-017 included two lower doses of continuous conjugated estrogens plus medroxyprogesterone acetate for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause. The two dosage strengths were 0.45 mg CE plus 1.5 mg MPA and 0.30 mg CE plus 1.5 mg MPA.

Study 0713D2-309-US (the HOPE Study), the clinical trial submitted in Supplement-017, was undertaken to satisfy a post-approval commitment to the FDA for Prempro™ 2.5 (approved in 1994) to determine the lowest effective dose of CE/MPA for the prevention of osteoporosis. This 8 arm, 24-month, double-dummy clinical trial includes 2,673 postmenopausal women who received one of the 4 following doses of CE plus MPA: 0.625 mg CE/2.5 mg MPA, 0.45 mg CE/2.5 mg MPA, 0.45 mg CE/1.5 mg MPA, and 0.30 CE/1.5 mg MPA; the corresponding doses of CE alone (0.625 mg, 0.45 mg, and 0.30 mg); and placebo. Subjects were randomly assigned doses and were instructed to take 2 tablets of the study medication daily (one active tablet and one matching placebo tablet or two matching placebo tablets) and one Caltrate tablet daily at approximately the same time each day. The Hope Study was comprised of a basic study (12 months, 13 cycles) and a metabolic/osteoporosis substudy (24 months, 26 cycles).

Supplement-017 was a 1-year interim analysis of the HOPE Study. The 12-month data from completed study year 1 (2153 subjects, 1,553 subjects in the basic study and 599 subjects ongoing in the metabolic/osteoporosis substudy) submitted in the S-017 application supported the safety and efficacy of the dose in reducing the incidence of estrogen-associated endometrial hyperplasia and in relieving moderate-to-severe hot flushes and vulvar and vaginal atrophy. The primary efficacy measurement for study year 1 was an assessment of the incidence of endometrial hyperplasia, made by endometrial biopsies conducted at baseline, 6 months and 12 months. Vasomotor symptoms and vaginal maturation indexes, assessed by evaluation of daily diaries and vaginal cytology smears, were secondary efficacy measurements.

On April 3, 2001, Wyeth-Ayerst withdrew the 0.3 mg CE/1.5 mg MPA dosage strength from consideration of approval without prejudice to refiling. The Division had the following concerns regarding the 0.3 mg CE/1.5 mg MPA dosage strength:

1. The efficacy of the 0.3 mg CE/1.5 mg MPA dosage strength for the subgroup of postmenopausal women < 50 years of age (statistically significant effectiveness for moderate-to-severe hot flushes was delayed to week 8).
2. The number of breast cancers found in the 0.3 mg CE/1.5 mg MPA dosage strength submitted with the 1-year interim data, the 120-Days Safety Update (dated 11/30/00), and the Second Safety Update (dated 5/15/01). A total of thirteen cases of breast cancer were reported in 2,673 treated subjects, 11 in active treatment groups and 2 in the placebo treatment group. Of the 11 cases of breast cancer in the active treatment groups, 4 occurred in CE-alone treatment groups and 7 in combination CE/MPA treatment groups. Four of the 7 combination CE/MPA treatment group cancers occurred in the 0.3 mg CE/1.5 mg MPA treatment group.
3. A less favorable lipid profile for the 0.3 mg CE/1.5 mg MPA dosage strength (mean percent increase in HDL-cholesterol and HDL_2-cholesterol from baseline were not significantly greater than placebo at cycle 13, mean percent decrease from baseline in LDL-cholesterol was not significantly greater than placebo, and mean percent increase from baseline triglycerides were similar to placebo).

This submission includes additional safety data from year-2 of Study 0713D2-309-US in support of the 0.3 mgCE/1.5 mg MPA dosage strength.

For the prevention of postmenopausal osteoporosis indication, Wyeth-Ayerst submitted a Type 6 NDA for the 0.3 mg CE/1.5 mg MPA and 0.45 mg CE/1.5 mg MPA dosage strengths to the Division of Metabolic and Endocrine Drug Products on September 25, 2001(NDA 21-396).

Fileability of Supplemental NDA 20-527/S-024

Supplemental NDA 20-527/S-024 is fileable.

Review Issues

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

Theresa H. van der Vlugt M.D., M.P.H.
Medical Officer

NDA: 20-527/S-024

45 Day Filing Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?	X		
2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
3) On its face, is the clinical section of the NDA legible so that substantive review can begin?	X		
4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	X		
5) On its face, do there appear to be the requisite number of adequate and well controlled studies in the application?	X		
6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	X		Study design for protection of the endometrium and the treatment of VVA was appropriate. However, for the treatment of vasomotor symptoms a subgroup analysis had to be performed due to the absence of appropriate inclusion criteria for the baseline number of moderate-to-severe hot flushes.
7) Are all data sets for pivotal efficacy studies complete for all indications (infections) requested?	X		
8) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X		

ITEM	YES	NO	COMMENT
9) Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?	X		
10) Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	NA		
11) Has the applicant submitted all additional required case record forms (beyond deaths and drop-puts) previously requested by the Division	X		
12) Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?	X		
13) Has the applicant presented safety assessment based on all current world-wide knowledge regarding this product?	X		
14) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?	X		
15) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	X		
16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	X		
17) Reasons for refusal to file:			

Theresa H. van der Vlugt, M.D., M.P.H.
Medical Officer

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

/s/

Theresa Van Der Vlugt
12/20/01 04:12:28 PM
MEDICAL OFFICER

Shelley Slaughter
12/20/01 04:30:39 PM
MEDICAL OFFICER
I concur

Meeting Minutes

Date: December 19, 2001 **Time:** 2:30 - 3:00 PM **Location:** Parklawn; Room 17 B43

NDA: 20-527/S-024 **Drug Name:** (conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) tablets, 0.3 CE/1.5mg MPA

Type of Meeting: Filing Meeting

Sponsor: Wyeth-Ayerst Research

Meeting Chair: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Shelley Slaughter, M.D., Ph.D. – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
David Lin, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, Division of Pharmaceutical Evaluation II (DPBII) @ DRUDP (HFD-580)
Moh-Jee Ng, M.S. – Statistician, Division of Biometrics II @ DRUDP (HFD-580)

Meeting Objective:
To discuss the fileability of Supplement 24 that proposes the new 0.03 mg CE/1.5 mg MPA dose for the treatment of moderate to severe vasomotor symptoms associated with the menopause and the treatment of vulvar and vaginal atrophy. The supplement incorporated a continuous, combined regimen.

Background: The Supplemental application was submitted on November 5, 2001, received November 7, 2001. The User Fee goal date is September 7, 2002. The sponsor has also submitted a supplemental NDA (NDA 21-396) for the same Prempro doses to the Division of Metabolism and Endocrine Drug Products for the prevention of postmenopausal osteoporosis. The User Fee goal date for that supplemental application is July 25, 2002.

Decisions reached:
- Regulatory
  - the DMEDP supplemental NDA reviews are scheduled for completion to the team leaders on May 24, 2002, with labeling discussions scheduled for June 12, 2002; the action package is due to the Division Director on July 8, 2002; DMEDP clinical review will be performed by Dr. Bruce Schneider
  - financial disclosure information is the same as previously submitted with Supplement S-017; review has been completed
  - the goal date for completion of all primary reviews for S-024 is commensurate with NDA 21-396 (May 24, 2002)
  - labeling discussion will be scheduled for April 2002

- Pharmacology
  - fileable, per pharmacology reviewer
  - since higher doses of these ingredients have been approved, Pharmacology has no toxicological concerns
- Tradename
  - no new tradename has been proposed
- Clinical
  - fileable
  - data for this supplemental application was reviewed in supplemental application S-115; an additional year of safety data was submitted with this application
- Biometrics
  - fileable
  - review of 1-year hyperplasia analysis will be reviewed
- DSI
  - no inspections have been requested for this supplement because both drug substances are approved drug substances for the intended indications and the same study data was used for Supplement S-115 (note: this study was conducted as a Phase 4 commitment at the time of the Prempro approval)
- Chemistry, Manufacturing and Quality Control
  - fileable
  - the manufacturing issues for the Premarin products have not changed
- Clinical Pharmacology and Biopharmaceutics
  - fileable
  - data submitted in this supplemental application has been reviewed in previously submitted applications

Action Items: none

Outstanding Items: none

Signature, minutes preparer

Concurrence, Chair

drafted: dm/12.31.01/N20527S24FM121901

Concurrence:
A.Jordan, M.Ng 1.2.02/S.Slaughter 1.8.02/T.van der Vlugt 1.14.02

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

/s/

Diane V. Moore
1/15/02 12:18:10 PM

Shelley Slaughter
1/15/02 04:02:00 PM
I concur.

ORIGINAL

WYETH-AYERST RESEARCH

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

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

RECEIVED
NOV 0 7 2001
CDR/CDER

NDA NO. 20527 REF. NO. SE1024
NDA SUPPL FOR Control

November 5, 2001

NDA 20-527
Prempro™ (conjugated estrogens/medroxyprogesterone acetate tablets)
Premphase® (conjugated estrogens/medroxyprogesterone acetate tablets)

Daniel Shames, MD, Acting 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. Shames:

Reference is made to our approved NDA 20-527 for Prempro™ / Premphase®(conjugated estrogens (CE) and medroxyprogesterone acetate (MPA) tablets).. In accordance with 21 CFR §314.50, Wyeth-Ayerst Laboratories hereby submits a supplemental New Drug Application for Prempro™ / Premphase® (CE/MPA). Prempro™ / Premphase® is approved for the treatment of moderate to severe vasomotor symptoms associated with menopause, the treatment of vulvar and vaginal atrophy, and the prevention of osteoporosis, with doses of 0.625mg CE/ 2.5 mg MPA and 0.625mg CE/ 5.0 mg MPA. Prempro™ is the trade name of the continuous combined regimen whereas Premphase® is a cyclic regimen.

Marketing approval is being sought for Prempro™ (0.3mg CE/1.5 mg MPA) in a continuous combined regimen for the treatment of moderate to severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy.

This supplemental NDA provides safety and effectiveness data regarding postmenopausal symptoms, endometrial hyperplasia, and metabolic parameters for the dose of 0.3mg CE/1.5mg MPA from Protocol No. 713B-309-US[1] (the HOPE study), *A Prospective, Double-Blind, Randomized Study of the Safety and Efficacy of Lower Doses of Premarin® and Medroxyprogesterone Acetate in Postmenopausal Women*. This NDA is not meant to satisfy the (b) (4) . This resubmission of Prempro™ CE 0.3mg/ MPA 1.5mg is the result of an option provided to Wyeth by DRUDP on March 30, 2001 for withdrawing CE 0.3mg/ MPA 1.5mg from the application NDA 20-527/ S-017 submitted on June 15,. 2000

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

without prejudice to refiling. The Division had the following concerns regarding the CE 0.3mg/ MPA 1.5mg strength: 1) efficacy of this strength for the subgroup of women close to menopause (<50 years of age) 2) the number of breast cancers found in this dosage group, and 3) a less favorable lipid profile for the CE 0.3mg/ MPA 1.5mg arm. We withdrew CE 0.3mg/ MPA 1.5mg from sNDA 20-527/ S-017 on April 3, 2001. Additional safety data from Year 2 of Protocol No. 713B-309-US (the HOPE study) in support of CE 0.3mg/MPA 1.5mg are included in this application.

For the prevention of osteoporosis indication, Wyeth-Ayerst has submitted a Type 3 NDA for the lower doses (CE 0.45mg/ MPA 1.5mg and CE 0.3mg/MPA 1.5mg) to the Division of Metabolic and Endocrine Drug Products (DMEDP) on September 25, 2001. This is the agreed upon procedure as directed by the two Divisions (DMEDP and DRUDP) in a teleconference on June 5, 2001. It was also noted by the FDA that the action on the pending application for the new lower strength of 0.45mg CE/1.5mg MPA (NDA 20-527/S-017, Approvable Letter dated April 13, 2001 issued by DRUDP) does not, in and of itself, preclude filing of this application. The Divisions agreed that Wyeth-Ayerst could submit this supplemental NDA since the sponsor is separately addressing the review issues cited in the April 13th Approvable Letter.

Clinical Study Background

During the October 1993 meeting with the Division of Metabolic and Endocrine Drug Products (DMEDP) to discuss the filing of NDA No. 20-303, [conjugated estrogens and medroxyprogesterone acetate (separate tablets)], Wyeth-Ayerst proposed to conduct a Phase IV clinical trial to define the minimum effective does of the combination of conjugated estrogens and medroxyprogesterone acetate for the prevention of osteoporosis. Several teleconferences and a face-to-face meeting were held with the Division to agree upon the final study design. The final protocol, 713B-309-US, was submitted on July 18, 1995.

This 8-arm, double blind (double-dummy), placebo and active-controlled, multi-center, outpatient trial was a 2-year study of lower-dose combinations of conjugated estrogens and medroxyprogesterone acetate in postmenopausal women. The purpose of this study was to determine whether a dose lower than 0.625 mg of Premarin® when combined with the daily administration of MPA might be effective in preventing post menopausal osteoporosis, reducing the incidence of endometrial hyperplasia, and relieving menopausal symptoms.

User Fee

User Fee ID No. 4140 has been assigned to this application. A check for 100% of the required fee ($154,823) for a supplement to a new drug application requiring clinical data review has been submitted to the Mellon Bank, Pittsburgh, PA postal address designated for user fee payments.

Field Copy

In compliance with 21 CFR §314.50(1)(3), a field copy of the chemistry, manufacturing and controls (CMC) was sent to the local district offices of the manufacturing facilities at Buffalo, New York (Mr. John Podsadowski) and San Juan, Puerto Rico (Mr. Jorge Guadalupe) on October 31, 2001. A copy was not sent to the Philadelphia District Office per Ms. Vlada Matusovsky's request on September 27, 2001.

Contents

All items in this NDA are provided as electronic files except for Item 5. The approximate size of the submission is 2.7 gigabytes and is contained on four (4) CD-ROMs. Some items are also included as paper and they are indicated in the table below. 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.

The contents are as follows:

Item No.	Description	Additional Paper Format
1	Table of Contents	
2	Labeling	
3	Summary	
4	Chemistry, Manufacturing, and Control	To field offices only
5	NonClinical Pharmacology and Toxicology	Reference to 20-303
6	Human Pharmacology and Bioavailability/Bioequivalence	
8	Clinstat	
11	Case Report Tabulation	
12	Case Report Forms	
13	Patent Information	Yes
14	Patent Certification	Yes
16	Debarment Certification	Yes
17	Field Copy Certification	Yes
18	User Fee Cover Sheet	Yes
19	Financial Information	Yes
20	Other	Yes

If you have any questions regarding this submission, please contact the undersigned at (484) 865-3749 or Cynthia Davidson at 484-865-3719.

Sincerely,

Jennifer D. Norman

Jennifer D. Norman, R. Ph.
Associate Director
Worldwide Regulatory Affairs
Women's Healthcare

Desk Copy: Ms. Diane Moore, Regulatory Project Manager, DRUDP
Dr. Samuel Wu, Regulatory Project Manager, DMEDP

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20527/S-024

PRIOR APPROVAL SUPPLEMENT

Wyeth-Ayerst Laboratories
Attention: Jennifer D. Norman, R.Ph.
Associate Director, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Norman:

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

Name of Drug Product:	Prempro™ (conjugated estrogens/medroxyprogesterone acetate) tablets, 0.3 mg CE/1.5mg MPA
NDA Number:	20-527
Supplement Number:	S-024
Review Priority Classification:	Standard (S)
Date of Supplement:	November 5, 2001
Date of Receipt:	November 7, 2001

This supplement proposes the following change: the addition of a 0.3 mg CE/1.5 mg MPA strength of Prempro™ in a continuous combined regimen for the treatment of moderate to severe vasomotor symptoms associated with the menopause, and the treatment of vulvar and vaginal atrophy.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 6, 2002, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 7, 2002.

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

U.S. Postal/Courier/Overnight Mail:

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

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Terri F. Rumble
11/29/01 11:04:16 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 20-527	Efficacy Supplement Type SE-1	Supplement Number 024
Drug:Prempro™ (conjugated estrogens/medroxyprogesterone acetate tablets)/Premprhase® (conjugated estrogens/medroxyprogesterone acetate tablets)/	Applicant: Wyeth Pharmaceuticals	
RPM: Kassandra Sherrod, R.Ph.	HFD-580	Phone # 301-827-4260
Application Type: (✓) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(✓) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	Sept. 12, 2003
❖ Special programs (indicate all that apply)	(✓) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(✓) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (✓) No
• This application is on the AIP	( ) Yes (✓) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(✓) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(✓) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) (✓) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity Summary (approvals only)	done
Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ Actions	
Proposed action	(✓) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE 8/28/02
• Status of advertising (approvals only)	(✓) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (✓) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(✓) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	✓
• Original applicant-proposed labeling	✓
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	✓
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	✓
• Reviews	✓
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	✓
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	~~MD 6/3/03~~ MTL - 8/28/02
❖ Clinical review(s) *(indicate date for each review)*	6/3/03
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	included in MO review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Statistical review(s) *(indicate date for each review)*	6/17/02
❖ Biopharmaceutical review(s) *(indicate date for each review)*	
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	8/21/02, 4/30/03
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: ( ) ~~Acceptable~~ ( ) Withhold recommendation
❖ Methods validation	( ) ~~Completed~~ ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

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

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

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

2. TELEPHONE NUMBER *(Include Area Code)*

(484) 865-3749

3. PRODUCT NAME

Prempro/Premphase (conjugated estrogens/ medroxyprogesterone acetate tablets)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 20-527

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

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

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4140

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

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

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

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

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

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

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

☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes 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

and

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

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Jennifer D. Norman, R.Ph. Jennifer D Norman	Associate Director Worldwide Regulatory Affairs	October 31, 2001

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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: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
20-527

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Wyeth-Ayerst Laboratories	November 5, 2001
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number *(Include Area Code)***
(484) 865-3749	(484) 865-9214
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 19101-8299	

PRODUCT DESCRIPTION

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

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
Conjugated Estrogens/Medroxyprogesterone Acetate Tablets	Prempro

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

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

(PROPOSED) INDICATION(S) FOR USE:
Treatment of moderate to sever vasomotor symptoms associated with menopause, and 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
Addition of lower dose

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

NUMBER OF VOLUMES SUBMITTED 4 CDROMs + 32 pages | 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)

NDA 20-303, approved NDA 20-527, approved NDA 04-782

DMF (b) (4) and DMF (b) (4)

	This application contains the following items: *(Check all that apply)*
☒	1. Index -- electronic
☒	2. Labeling (check one) ☒ Draft Labeling -- electronic ☐ Final Printed Labeling
☒	3. Summary (21 CFR 314.50 (c)) -- electronic
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2) --electronic
☐	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) -- electronic
☐	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) -- electronic
☒	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2) -- electronic
☒	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2) – electronic
☒	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2) -- electronic
☒	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2) – electronic
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c)) – paper and electronic
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A)) – paper and electronic
☐	15. Establishment description (21 CFR Part 600, if applicable)
☒	16. Debarment certification (FD&C Act 306 (k)(1)) -- paper and electronic
☒	17. Field copy certification (21 CFR 314.5 (k) (3)) -- paper and electronic
☒	18. User Fee Cover Sheet (Form FDA 3397) -- paper and electronic
☒	19. Financial Information (21 CFR Part 54) -- paper and electronic
☒	20. OTHER (Specify) Pediatric Rule, paper and electronic

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, R.Ph., Associate Director, Worldwide Regulatory Affairs	11/05/01

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
P.O Box 8299, Philadelphia,PA 19101-8299	(484) 865-3749

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