CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 020527/S-046

Trade Name: PREMPRO

Generic Name: Conjugated Estrogens/Medroxyprogesterone Acetate Tablets

Sponsor: Wyeth Pharmaceuticals Inc.

Approval Date: 05/18/2009

Indications: 1. Treatment of moderate to severe vasomotor symptoms due to menopause.

2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause.

3. Prevention of postmenopausal osteoporosis. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020527/S-046

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letter(s)	**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	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020527/S-046

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-527/S-046

Wyeth Pharmaceuticals Inc.
Attention: Christian D. Le
Sr. Regulatory Specialist, Global Regulatory Affairs, CMC
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Le:

Please refer to your supplemental new drug application (sNDA) dated and received June 25, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prempro® 0.3 mg/1.5 mg and 0.45 mg/1.5 mg (conjugated estrogens/medroxyprogesterone acetate tablets).

We also acknowledge receipt of your submissions dated September 12, October 20, December 23, 2008, April 22 (2), and May 18, 2009.

Your submission of December 23, 2008, constituted a complete response to our December 15, 2008, action letter.

This supplemental new drug application provides for:

1. Reformulation of Prempro® 0.3 mg/1.5 mg and 0.45 mg/1.5 mg (conjugated estrogens/medroxyprogesterone acetate tablets).
2. Revisions to the **DESCRIPTION, Pharmacokinetics** subsection (Table 2) of **CLINICAL PHARMACOLOGY**, and **HOW SUPPLIED** sections of the Physician Package Insert to incorporate information on reformulated Prempro® 0.3 mg/1.5 mg and 0.45 mg/1.5 mg tablets.
3. Revisions to the Patient Information Insert under **"What are the ingredients in Prempro and Premphase?"** to incorporate information on the reformulated Prempro® 0.3 mg/1.5 mg and 0.45 mg/1.5 mg tablets.
4. A new 28-day Blister card, revisions to the Carton and Bottle labels, and new NDC numbers for Prempro® 0.3 mg/1.5 mg and 0.45 mg/1.5 mg tablets.
5. Change of the ™ symbol after Prempro to a ® symbol in all occurrences.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed, agreed-upon labeling. Upon receipt, we will transmit that version to the National Library of Medicine for public

dissemination. For administrative purposes, please designate this submission "**SPL for approved NDA 20-527/S-046**."

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 George Lyght, R.Ph., Sr. Regulatory Health Project Manager, at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic 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/

Scott Monroe

5/18/2009 04:17:04 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020527/S-046

OTHER ACTION LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-527/S-046

COMPLETE RESPONSE

Wyeth Pharmaceuticals Inc.
Attention: Christian D. Le
Sr. Regulatory Specialist, Global Regulatory Affairs, CMC
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Le:

Please refer to your supplemental new drug application (sNDA) dated and received June 25, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prempro™ and Premphase® (conjugated estrogens/medroxyprogesterone acetate tablets).

We acknowledge receipt of your amendments dated September 12, and October 20, 2008.

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

Clinical Pharmacology

Data to support the long-term stability of medroxyprogesterone acetate (MPA) in stored samples were not provided. Provide such data (i.e., sample stability study report) for review.

Chemistry, Manufacturing, and Controls (CMC)

1. Provide a statement regarding which submission to the NDA provides the approved MPA dissolution method (L18623-045).
2. Provide a side by side comparison of the proposed MPA dissolution method (L26403-009) and the approved MPA dissolution method (L18623-045).
3. To support the newly proposed MPA dissolution method, provide the study report to justify the use of the apparatus, dissolution medium, pH, and agitation speed. Additionally, provide supporting data that the method is discriminatory.
4. With a suitably justified dissolution method, provide (1) dissolution data for the reformulated batches and (2) dissolution profile comparisons between the reformulated 0.30 mg Premarin/1.5 mg MPA batches and the reformulated 0.45 mg Premarin/1.5 mg MPA batch used in the bioequivalence (BE) study. Provide the raw dissolution data (with at least 12 individual dosage units and the percent coefficient of variation at each time point) and dissolution profile comparisons with f2 calculations. Perform the f2

calculations according to the CDER Guidance with use of not more than one data point past (b) (4)% dissolved.

5. Limited dissolution data provided in the supplement for the six batches (average and range of dissolution values) do not support the proposed acceptance criterion of (b) (4) MPA at 30 minutes and (b) (4) MPA at 90 minutes. Provide the raw dissolution data (with at least 12 individual dosage units and the percent coefficient of variation at each time point) to support the proposed acceptance criteria for the 30 minute and 90 minute time points.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

If you have any questions, call George Lyght, R.Ph., Sr. Regulatory Health Project Manager, at 301-796-0948.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic 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/

Scott Monroe

12/15/2008 11:29:28 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020527/S-046

LABELING

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

Rx only

WARNINGS

CARDIOVASCULAR AND OTHER RISKS

Estrogens plus progestins should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders** and **Dementia**.)

The estrogen plus progestin substudy of the Women's Health Initiative (WHI) reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg), relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders** and **Malignant neoplasms, Breast cancer**.)

The estrogen alone substudy of the WHI reported increased risks of stroke and DVT in postmenopausal women (50 to 79 years of age) during 6.8 years and 7.1 years, respectively, of treatment with daily CE 0.625 mg, relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders**.)

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE 0.625 mg combined with MPA 2.5 mg and during 5.2 years of treatment with daily CE 0.625 mg alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES**, and **WARNINGS, Dementia** and **PRECAUTIONS, Geriatric Use**.)

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA and other combinations and dosage forms of estrogens and progestins. 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.

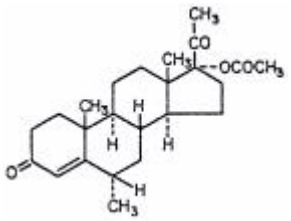
PREMPRO 0.625 mg/2.5 mg therapy consists of a single tablet containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 2.5 mg of medroxyprogesterone acetate for oral administration.

PREMPRO 0.625 mg/5 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.

Premarin (conjugated estrogens tablets, USP) for oral administration contains a mixture 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. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains 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, microcrystalline cellulose, hypromellose, hydroxypropyl cellulose, sucrose, Eudragit NE 30D, lactose monohydrate, magnesium stearate, polyethylene glycol, povidone, titanium dioxide, yellow iron oxide, and iron oxide black.

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, microcrystalline cellulose, hypromellose, hydroxypropyl cellulose, sucrose, Eudragit NE 30D, lactose monohydrate, magnesium stearate, polyethylene glycol, povidone, titanium dioxide, yellow iron oxide, and iron oxide black.

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, and black iron 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, and black iron oxide.

PREMPHASE
Each maroon Premarin tablet for oral administration contains 0.625 mg of conjugated estrogens and the following inactive ingredients: calcium phosphate tribasic, hydroxypropyl cellulose, microcrystalline cellulose, powdered cellulose, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, sucrose, titanium dioxide, FD&C Blue No. 2, and FD&C Red No. 40. These tablets comply with USP Dissolution Test 5.

Each light-blue tablet for oral administration contains 0.625 mg of 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, and black iron oxide.

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

A. Absorption

Conjugated estrogens are water-soluble 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 4 PREMPRO 0.45 mg/1.5 mg tablets to healthy, postmenopausal women.

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

DRUG	4 x 0.45 mg CE/1.5 mg MPA Combination (n = 65)			
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (pg/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (pg•h/mL)
Unconjugated Estrogens				
Estrone	149 (35)	8.9 (35)	37.5 (35)	6641 (39)
BA* -Estrone	130 (40)	8.9 (35)	21.2 (35)	3799 (47)
Equilin	83 (38)	8.3 (48)	15.9 (44)	1889 (40)
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Conjugated Estrogens				
Total Estrone	5.4 (49)	7.9 (48)	22.4 (53)	119 (48)
BA* -Total Estrone	5.2 (48)	7.9 (48)	15.1 (29)	100 (47)
Total Equilin	4.3 (42)	6.5 (45)	11.6 (31)	74 (48)
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Medroxyprogesterone Acetate				
MPA	0.7 (66)	2.0 (52)	26.2 (35)	5.0 (61)

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 percent and increased total equilin C_{max} by 38 percent 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 percent.

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.

B. 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.

C. 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 intestine 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 occur primarily in the liver via hydroxylation, with subsequent conjugation and elimination in the urine.

D. 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.

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

F. 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 2,805 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 seven 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, LAST OBSERVATION CARRIED FORWARD (LOCF)

Treatment[a] (No. of Patients)	----------No. of Hot Flushes/Day----------			
Time Period (week)	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 1,376 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 percent) and in the PREMPHASE treatment group (less than 1 percent; 1 percent when focal hyperplasia was included) compared to the Premarin group (8 percent; 20 percent 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, 2,001 women (average age 53.3 ± 4.9 years) of whom 88 percent 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.

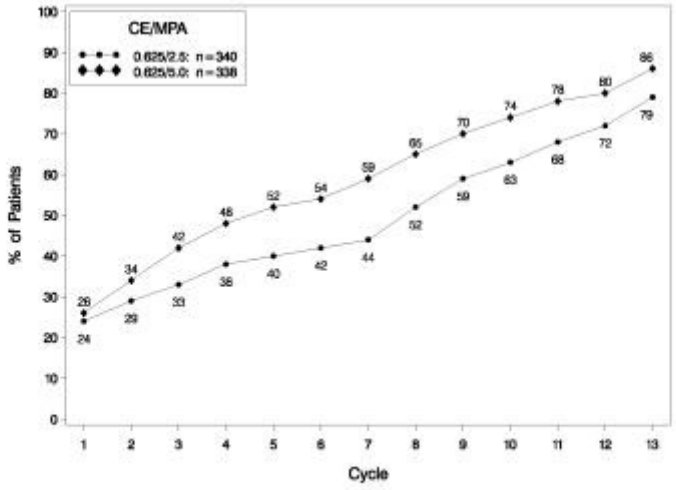


FIGURE 1. PATIENTS WITH CUMULATIVE AMENORRHEA OVER TIME PERCENTAGES OF WOMEN WITH NO BLEEDING OR SPOTTING AT A GIVEN CYCLE THROUGH CYCLE 13 INTENT-TO-TREAT POPULATION, LOCF

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).

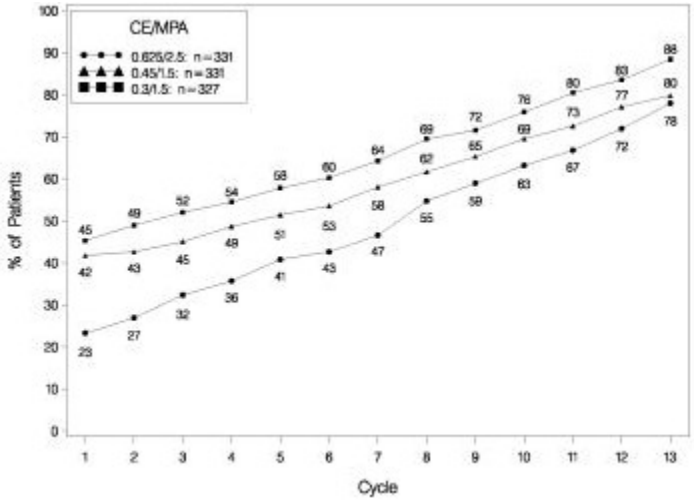


FIGURE 2. PATIENTS WITH CUMULATIVE AMENORRHEA OVER TIME PERCENTAGES OF WOMEN WITH NO BLEEDING OR SPOTTING AT A GIVEN CYCLE THROUGH CYCLE 13 INTENT-TO-TREAT POPULATION, LOCF

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 four 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 percent with 0.625 mg/2.5 mg, 2.18 percent with 0.45 mg/1.5 mg, and 1.71 percent with 0.3 mg/1.5 mg. The placebo group showed a mean percent decrease from baseline at the final evaluation of 2.45 percent. 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 three 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 three 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, LOCF

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.

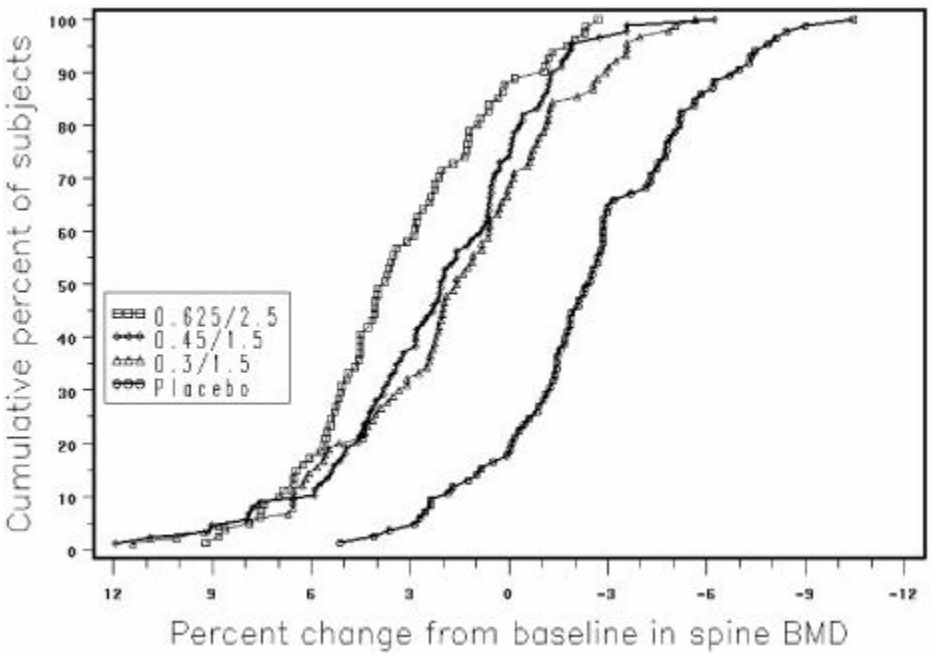


FIGURE 3. CUMULATIVE PERCENT OF SUBJECTS WITH CHANGES FROM BASELINE IN SPINE BMD OF GIVEN MAGNITUDE OR GREATER IN PREMARIN/MPA AND PLACEBO GROUPS

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.

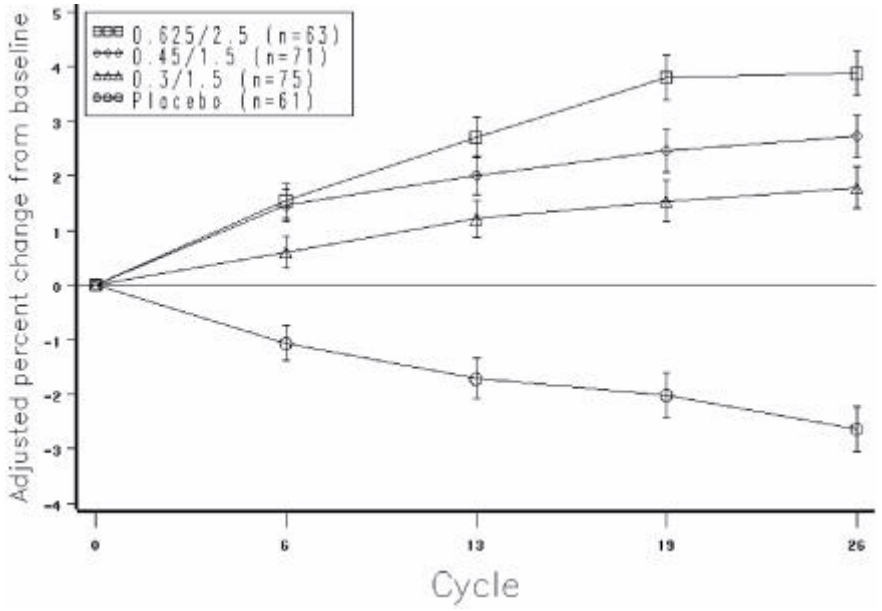


FIGURE 4. ADJUSTED MEAN (SE) PERCENT CHANGE FROM BASELINE AT EACH CYCLE IN SPINE BMD: SUBJECTS COMPLETING IN PREMARIN/MPA GROUPS AND PLACEBO

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

The Women's Health Initiative (WHI) enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of either the use of daily oral conjugated estrogens (CE 0.625 mg) alone or in combination with medroxyprogesterone acetate (MPA 2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction [MI], silent MI and CHD death), with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer (only in CE/MPA substudy), colorectal cancer, hip fracture, or death due to other causes. The study did not evaluate the effects of CE/MPA or CE on menopausal symptoms.

The estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.2 years of treatment, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years (relative risk [RR] 1.15, 95 percent nominal confidence interval [nCI] 1.03-1.28).

For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE/MPA were 6 more CHD events, 7 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 7 fewer colorectal cancers and 5 fewer hip fractures. (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

Results of the estrogen plus progestin substudy, which included 16,608 women (average age 63 years, range 50 to 79; 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 8. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

TABLE 8. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN PLUS PROGESTIN SUBSTUDY OF WHI AT AN AVERAGE OF 5.6 YEARS[a]

Event	Relative Risk CE/MPA vs. Placebo (95% nCI[b])	Placebo n = 8,102	CE/MPA n = 8,506
		Absolute Risk per 10,000 Women-Years	
CHD events	1.24 (1.00–1.54)	33	39
Non-fatal MI	*1.28 (1.00–1.63)*	*25*	*31*
CHD death	*1.10 (0.70–1.75)*	*8*	*8*
All Strokes	1.31 (1.02–1.68)	24	31
Ischemic stroke	*1.44 (1.09–1.90)*	*18*	*26*
Deep vein thrombosis	1.95 (1.43–2.67)	13	26
Pulmonary embolism	2.13 (1.45–3.11)	8	18
Invasive breast cancer[c]	1.24 (1.01–1.54)	33	41
Invasive colorectal cancer	0.56 (0.38–0.81)	16	9
Endometrial cancer	0.81 (0.48–1.36)	7	6
Cervical cancer	1.44 (0.47–4.42)	1	2
Hip fracture	0.67 (0.47–0.96)	16	11
Vertebral fractures	0.65 (0.46–0.92)	17	11
Lower arm/wrist fractures	0.71 (0.59–0.85)	62	44
Total fractures	0.76 (0.69–0.83)	199	152

[a]Results are based on centrally adjudicated data. Mortality data was not part of the adjudicated data, however data at 5.2 years of follow-up showed no difference between the groups in terms of all-cause mortality (RR 0.98, 95 percent nCI 0.82-1.18).
[b]Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[c]Includes metastatic and non-metastatic breast cancer, with the exception of in situ breast cancer.

The estrogen alone substudy was also stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen alone in predetermined primary endpoints. Results of the estrogen alone substudy, which included 10,739 women (average age of 63 years, range 50 to 79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other) after an average follow-up of 6.8 years, are presented in Table 9.

TABLE 9. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN ALONE ONE SUBSTUDY OF WHI[a]

Event	Relative Risk CE vs. Placebo (95% nCI[a])	Placebo n = 5,310	CE n = 5,429
		Absolute Risk per 10,000 Women-Years	
CHD events[b]	0.95 (0.79–1.16)	56	53
Non-fatal MI[b]	*0.91 (0.73–1.14)*	*43*	*40*
CHD death[b]	*1.01 (0.71–1.43)*	*16*	*16*
Stroke[b]	1.37 (1.09–1.73)	33	45
Ischemic[b]	*1.55 (1.19-2.01)*	*25*	*38*
Deep vein thrombosis[b,d]	1.47 (1.06–2.06)	15	23
Pulmonary embolism[b]	1.37 (0.90–2.07)	10	14
Invasive breast cancer[b]	0.80 (0.62–1.04)	34	28
Colorectal cancer[c]	1.08 (0.75–1.55)	16	17
Hip fracture[c]	0.61 (0.41–0.91)	17	11
Vertebral fractures[c,d]	0.62 (0.42–0.93)	17	11
Total fractures[c,d]	0.70 (0.63–0.79)	195	139
Death due to other causes[c,e]	1.08 (0.88–1.32)	50	53
Overall mortality[c,d]	1.04 (0.88–1.22)	78	81
Global Index[c,f]	1.01 (0.91–1.12)	190	192

[a]Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[b]Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
[c]Results are based on an average follow-up of 6.8 years.
[d]Not included in Global Index.
[e]All deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease.
[f]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, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE alone were 12 more strokes while the absolute risk reduction per 10,000 women-years was 6 fewer hip fractures. The

absolute excess risk of events included in the "global index" was a nonsignificant 2 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

Final centrally adjudicated results for CHD events and centrally adjudicated results for invasive breast cancer incidence from the estrogen alone substudy, after an average follow-up of 7.1 years, reported no overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE alone compared with placebo (see Table 9).

Centrally adjudicated results for stroke events from the estrogen alone substudy, after an average follow-up of 7.1 years, reported no significant difference in distribution of stroke subtype or severity, including fatal strokes, in women receiving CE alone compared to placebo. Estrogen alone increased the risk of ischemic stroke, and this excess was present in all subgroups of women examined (see Table 9).

Women's Health Initiative Memory Study

The estrogen plus progestin Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent, age 65 to 69 years; 35 percent, 70 to 74 years; 18 percent, 75 years of age and older) to evaluate the effects of daily CE/MPA 0.625 mg conjugated estrogens/2.5 mg medroxyprogesterone acetate on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the estrogen plus progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95 percent CI 1.21–3.48) compared to placebo. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS**, **WARNINGS, Dementia** and **PRECAUTIONS, Geriatric Use**.)

The estrogen alone WHIMS substudy enrolled 2,947 predominantly healthy postmenopausal women 65 years of age and older (45 percent, age 65 to 69 years; 36 percent, 70 to 74 years; 19 percent, 75 years of age and older) to evaluate the effects of daily CE 0.625 mg on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen alone group (37 per 10,000 women-years) and 19 in the placebo group (25 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the estrogen alone group was 1.49 (95 percent CI 0.83–2.66) compared to placebo. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS**, **WARNINGS, Dementia** and **PRECAUTIONS, Geriatric Use**.)

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown

whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS**, **WARNINGS, Dementia** and **PRECAUTIONS, Geriatric Use**.)

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 due to menopause.

2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to 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 for whom non-estrogen medications are not considered to be appropriate. (See **CLINICAL STUDIES**.)

   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
PREMPRO or PREMPHASE therapy 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 (within past year) arterial thromboembolic disease (for example, stroke, myocardial infarction).

6. Liver dysfunction or disease.

7. Known hypersensitivity to any of the ingredients in PREMPRO or PREMPHASE.

8. Known or suspected pregnancy.

WARNINGS
See **BOXED WARNINGS**.

1. Cardiovascular disorders
An increased risk of stroke, deep vein thrombosis (DVT), pulmonary embolism, and myocardial infarction has been reported with estrogen plus progestin therapy.

An increased risk of stroke and DVT has been reported with estrogen alone therapy.

Should any of these events occur or be suspected, estrogens with or without progestins should be discontinued immediately.

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

a. Stroke
In the Women's Health Initiative (WHI) estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women receiving daily conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) compared to placebo (31 versus 24 per 10,000 women-years). The increase in risk was demonstrated after the first year and persisted. (See **CLINICAL STUDIES**.)

In the estrogen alone substudy of the WHI, a statistically significant increased risk of stroke was reported in women receiving daily CE 0.625 mg compared to placebo (44 versus 32 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted. (See **CLINICAL STUDIES**.)

b. Coronary heart disease
In the estrogen plus progestin substudy of WHI, no statistically significant increase of CHD events (defined as nonfatal MI, silent MI, or death, due to CHD) was reported in women receiving CE/MPA compared to placebo (39 versus 33 per 10,000 women years). An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5. (See **CLINICAL STUDIES**.)

In the estrogen alone substudy of WHI, no overall effect on coronary heart disease (CHD) events was reported in women receiving estrogen alone compared to placebo. (See **CLINICAL STUDIES**.)

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/progestin Replacement Study; HERS), treatment with daily CE 0.625 mg/MPA 2.5 mg demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year one, but not during the subsequent years. Two thousand three hundred and twenty one (2,321) 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 CE/MPA group and the placebo group in the HERS, the HERS II, and overall.

c. Venous thromboembolism (VTE)
In the estrogen plus progestin substudy of WHI, a statistically significant 2-fold greater rate of VTE (DVT and pulmonary embolism [PE]), was reported in women receiving daily CE/MPA compared to placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted. (See **CLINICAL STUDIES**.)

In the estrogen alone substudy of WHI, the risk of VTE was reported to be increased for women receiving daily CE compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women years). The increase in VTE risk was demonstrated during the first 2 years. (See **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
The most important randomized clinical trial providing information about this issue in estrogen plus progestin users is the Women's Health Initiative (WHI) substudy of daily conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg). In the estrogen plus progestin substudy, after a mean follow-up of 5.6 years, the WHI substudy reported an increased risk of breast cancer in women who took daily CE/MPA. In this substudy, prior use of estrogen alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24 (95 percent nominal confidence interval [nCI] 1.01-1.54), and the absolute risk was 41 versus 33 cases per 10,000 women-years, for estrogen plus progestin compared with placebo, respectively. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for estrogen plus progestin compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for estrogen plus progestin compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups. (See **CLINICAL STUDIES**.)

The most important randomized clinical trial providing information about this issue in estrogen alone users is the Women’s Health Initiative (WHI) substudy of daily CE 0.625 mg. In the estrogen alone substudy of WHI, after an average of 7.1 years of follow-up, daily CE 0.625 mg

was not associated with an increased risk of invasive breast cancer (RR 0.80, 95 percent nCI 0.62-1.04). (See **CLINICAL STUDIES**.)

The results from observational studies are generally consistent with those of the WHI clinical trial. Observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogens or among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

b. Endometrial cancer
An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in women with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times 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 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 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 using estrogen plus progestin therapy 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 percent 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. Dementia
In the estrogen plus progestin Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) or

placebo. In the estrogen alone WHIMS substudy, a population of 2,947 hysterectomized women 65 to 79 years of age, was randomized to daily CE 0.625 mg or placebo.

In the estrogen plus progestin substudy, after an average follow-up of 4 years, 40 women in the CE/MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE/MPA versus placebo was 2.05 (95 percent CI 1.21-3.48). The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years. (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use**.)

In the estrogen alone substudy, after an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE alone versus placebo was 1.49 (95 percent CI 0.83-2.66). The absolute risk of probable dementia for CE alone versus placebo was 37 versus 25 cases per 10,000 women-years. (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use**.)

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI 1.19-2.60). Since both substudies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS** and **PRECAUTIONS, Geriatric Use**.)

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

5. 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.

6. 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 permanently 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 (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. Consider discontinuation of treatment if pancreatitis or other complications develop.

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
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
The estrogen plus progestin substudy of WHI reported a non-statistically significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95 percent nCI 0.77 – 3.24). The absolute risk for CE/MPA versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure

associated with increased risk is not consistent across all epidemiologic studies and some report no association.

9. Exacerbation of endometriosis
Endometriosis may be exacerbated with administration of estrogen therapy.

A few cases of malignant transformation of residual endometrial implants has been reported in women treated post-hysterectomy with estrogen alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

10. Exacerbation of other conditions
Estrogen therapy 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
Serum follicle stimulating hormone and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy.

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 total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. 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. Aminoglutethimide administered concomitantly with medroxyprogesterone acetate (MPA) may significantly depress the bioavailability of MPA.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility
(See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

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.

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
PREMPRO and PREMPHASE should not be used during lactation. 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.

H. Pediatric Use
PREMPRO and PREMPHASE are not indicated for pediatric use and no clinical data have been collected in children.

I. Geriatric Use
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.

Of the total number of subjects in the estrogen plus progestin substudy of the Women's Health Initiative (WHI) study, 44 percent (n=7,320) were 65 years of age and older, while 6.6 percent (n=1,095) were 75 years and older. In women 75 years of age and older compared to women less than 74 years of age, there was a higher relative risk of nonfatal stroke and invasive breast cancer in the estrogen plus progestin group versus placebo. In women greater than 75, the increased risk of nonfatal stroke and invasive breast cancer observed in the estrogen plus progestin group compared to placebo was 75 versus 24 per 10,000 women-years and 52 versus 12 per 10,000 women-years, respectively.

In the estrogen plus progestin substudy of the Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 4,532 hysterectomized women, 65 to 79 years of age, was randomized to daily CE 0.625 mg/MPA 2.5 mg or placebo. In the estrogen plus progestin group, after an average follow-up of 4 years, the relative risk (CE/MPA versus placebo) of probable dementia was 2.05 (95 percent CI 1.21-3.48). The absolute risk of developing probable dementia with CE/MPA was 45 versus 22 cases per 10,000 women-years with placebo.

Of the total number of subjects in the estrogen alone substudy of WHI, 46 percent (n=4,943) were 65 years of age and older, while 7.1% (n=767) were 75 years of age and older. There was a higher relative risk (daily CE versus placebo) of stroke in women less than 75 years of age compared to women 75 years and older.

In the estrogen alone WHIMS substudy, a population of 2,947 hysterectomized women, 65 to 79 years of age, was randomized to daily CE 0.625 mg or placebo. After an average follow-up of 5.2 years, the relative risk (CE versus placebo) of probable dementia was 1.49 (95 percent CI 0.83-2.66). The absolute risk of developing probable dementia with estrogen alone was 37 versus 25 cases per 10,000 women-years compared with placebo.

Seventy-nine percent of the cases of probable dementia occurred in women that were older than 70 for the CE alone group, and 82 percent of the cases of probable dementia occurred in women who were older than 70 in the CE/MPA group. The most common classification of probable dementia in both the treatment groups and placebo groups was Alzheimer’s disease.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI 1.19-2.60). Since both substudies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS** and **WARNINGS, Dementia**.)

ADVERSE REACTIONS
See **BOXED WARNINGS**, **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.

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 10).

TABLE 10. ALL TREATMENT EMERGENT STUDY EVENTS REGARDLESS OF DRUG RELATIONSHIP REPORTED AT A FREQUENCY ≥ 5%

Body System Adverse event	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%

TABLE 10. ALL TREATMENT EMERGENT STUDY EVENTS REGARDLESS OF DRUG RELATIONSHIP REPORTED AT A FREQUENCY ≥ 5%

Body System Adverse event	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)
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 2,333 postmenopausal women between 40 and 65 years of age (88% Caucasian), 2,001 women 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 11 summarizes adverse events that occurred at a rate ≥ 5% in at least 1 treatment group.

TABLE 11. 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%

TABLE 11. 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)
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%
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%

TABLE 11. 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)
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
Abnormal uterine bleeding/spotting, dysmenorrhea/pelvic pain, 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, for example, retinal vascular thrombosis and optic neuritis, intolerance of contact lenses.

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

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
Overdosage of estrogen/progestin may cause nausea and vomiting, breast tenderness, abdominal pain, drowsiness/fatigue and withdrawal bleeding may occur in females. Treatment of overdose consists of discontinuation of PREMPRO or PREMPHASE together with institution of appropriate symptomatic care.

DOSAGE AND ADMINISTRATION
Use of estrogens, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (for example, at 3-month to 6-month intervals) to determine if treatment is still necessary (see **BOXED WARNINGS** 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.

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.

1. For treatment of moderate to severe vasomotor symptoms and/or moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. When prescribing solely for the treatment of symptoms of moderate to severe 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 for whom non-estrogen medications are not considered to be appropriate.

- 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.

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

PREMPRO 0.3 mg/1.5 mg
Each carton contains 1 blister card containing 28 tablets. One blister card contains 28 oval, cream tablets. Each tablet contains 0.3 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg medroxyprogesterone acetate for oral administration (NDC 0046-1105–11).

Each bottle contains 90 oval, cream tablets. Each tablet contains 0.3 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg medroxyprogesterone acetate for oral administration (NDC 0046–1105–21).

PREMPRO 0.45 mg/1.5 mg
Each carton includes 1 blister card containing 28 tablets. One blister card contains 28 oval, gold tablets. Each tablet contains 0.45 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg medroxyprogesterone acetate for oral administration (NDC 0046-1106–11).

Each bottle contains 90 oval, gold tablets. Each tablet contains 0.45 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg medroxyprogesterone acetate for oral administration (NDC 0046–1106–21).

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. Each tablet contains 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. Each tablet contains 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 1 blister pack containing 28 tablets. One blister pack 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 0046-2579-11).

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 trademark.

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

United States Patent Number: 5,547,948 (PREMPRO).

PATIENT INFORMATION
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, strokes, or dementia.

Using estrogens and progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots. Using estrogens, with or without progestins, may increase your chance of getting dementia, based on a study of women age 65 years or older. 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. If you use PREMPRO or PREMPHASE only to treat your dryness, itching, and burning in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.

- **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 due to 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 of 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 (womb) removed (hysterectomy).

PREMPRO and PREMPHASE contain a progestin to decrease the chance 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.**

- **Currently have or have had 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 at the lowest dose possible for your treatment only as long as needed. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with PREMPRO or PREMPHASE.

What are the possible side effects of PREMPRO or PREMPHASE?

Side effects are grouped by how serious they are and how often they happen when you are treated.

Serious but less common side effects:

- Breast cancer

- Cancer of the uterus

- Stroke

- Heart attack

- Blood clots

- Dementia

- Gallbladder disease

- Ovarian cancer
- High blood pressure
- Liver problems
- High blood sugar
- Enlargement of benign tumors of the uterus ("fibroids")
- Mental depression

Some of the warning signs of these serious side effects include:

- 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
- Yellowing of the skin, eyes or nail beds

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

Less serious but common side effects include:

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

- Hair loss
- Fluid retention
- Vaginal yeast infection

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 and 17β-dihydroequilin. PREMPRO also contains either 1.5, 2.5, or 5 mg of medroxyprogesterone acetate.

PREMPRO 0.3 mg/1.5 mg and 0.45 mg/1.5 mg also contain calcium phosphate tribasic, microcrystalline cellulose, lactose monohydrate, hydromellose, magnesium stearate,

polyethylene glycol, sucrose, hydroxypropyl cellulose, Eudragit NE 30D, povidone, titanium dioxide, yellow iron oxide, and iron oxide black.

PREMPRO 0.625 mg/2.5 mg and 0.625 mg/5 mg also contain calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, black iron oxide, and FD&C Blue No. 2 or red ferric oxide.

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, hydroxypropyl cellulose, microcrystalline cellulose, powdered cellulose, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, sucrose, titanium dioxide, FD&C Blue No. 2, 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, and black iron oxide.

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

PREMPRO 0.3 mg/1.5 mg
Each carton includes 1 blister card containing 28 tablets. One blister card contains 28 oval, cream tablets. Each tablet contains 0.3 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg of medroxyprogesterone acetate for oral administration.

Each bottle contains 90 oval, cream tablets. Each tablet contains 0.3 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg medroxyprogesterone acetate for oral administration.

PREMPRO 0.45 mg/1.5 mg
Each carton includes 1 blister card containing 28 tablets. One blister card contains 28 oval, gold tablets. Each tablet contains 0.45 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg of medroxyprogesterone acetate for oral administration.

Each bottle contains 90 oval, gold tablets. Each tablet contains 0.45 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg 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. Each tablet contains 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. Each tablet contains 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 1 blister pack containing 28 tablets. One blister pack 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 trademark.

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

United States Patent Number: 5,547,948 (PREMPRO).

This product's label may have been updated. For current package insert and further product information, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

Wyeth®

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

(Update W10407C021)
(Update ET01)
Revised May 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020527/S-046

MEDICAL REVIEW(S)

Medical Officer's Review of the Labeling Submitted in NDA 20-527/SCF-046

TO:	NDA 20-527
FROM:	Theresa H. van der Vlugt, MD, M.P.H. Medical Officer Division of Reproductive and Urologic Products
THROUGH:	Shelley Slaughter, MD, Ph.D. Medical Team Leader Division of Reproductive and Urologic Products
SUBJECT:	Supplement - Prior Approval Supplement for a Reformulation of PREMPRO™ (conjugated estrogens/medroxyprogesterone acetate tablets) 0.45 mg/1.5 mg and 0.3 mg/1.5 mg
DATE:	April 23, 2009

Background:

PREMPRO™ (conjugated estrogens/medroxyprogesterone acetate tablet) 0.45 mg/1.5 mg was approved on March 12, 2003 (NDA 20-527/S-017). (b) (4)

NDA 20-527/SCF-046, submitted on June 25. 2008, provided chemistry, manufacturing, and controls (CMC) information for the reformulated low dose PREMPRO™ products (0.3 mg/1.5 mg and 0.45 mg/1.5 mg) and a final report on the pivotal bioequivalence study, CSR 72630, Protocol Number: 0713E1-1142-US, "An Open-Label, Single-Dose, Randomized, 4-period, Crossover, Bioequivalence Study of three New Formulations of Premarin 0.45 mg/medroxyprogesterone Acetate (MPA) 1.5 mg Compared With a Reference Formulation of Premarin/MPA (Prempro™) 0.45 mg/1.5 mg in Healthy Postmenopausal Women." A waiver for conducting a bioequivalence study on the reformulated 0.3 mg/1.5 mg tablet was granted by the Agency on December 21, 2006.

Office of Clinical Pharmacology Review:

Per the Clinical Pharmacology Review, dated February 20, 2009, the "new formulation of Prempro 0.45 mg/1.5 mg was found to be equivalent to the currently approved formulation of the same tablet strength."

Recommendation:

"The Office of Clinical pharmacology/Division of Clinical Pharmacology 3 finds the Clinical Pharmacology of NDA 20-527/S-046 acceptable."

ONDQA-DPE Chemistry Review:

The request for a biowaiver for the 0.3 mg/1.5 mg reformulated PREMPRO™ was previously granted pending a demonstration of bioequivalence for the reformulated 0.45 mg/1.5 mg Prempro. However, the ONDQA-Biopharmaceutics Reviewer evaluated the dissolution data to determine if the biowaiver was justified and found deficiencies with the dissolution method.

Based on data obtained up to 9 months at 25C and on data obtained from a statistical analysis, the ONDQA-Biopharmaceutics Reviewer determined that the data supported the following acceptance criteria:

Time	% MPA Dissolved
30 minutes	(b) (4) %
90 minutes	(b) (4) %

The Sponsor was notified of this, and responded with the amendment dated 22-Apr-2009, which provided an analysis of the release and stability data for the six batches, three 0.3 mg/1.5 mg and three 0.45 mg/1.5 mg. The analysis shows that if the FDA proposed limits at 30 minutes are used, then a significant amount of Stage 2 testing is required. Wyeth Pharmaceuticals Inc. proposed, alternatively, the limits of (b) (4) % at 30 minutes. The FDA proposed limit of (b) (4) % at 90 minutes was acceptable to the Sponsor.

CMC also evaluated the proposed Carton, Bottle label, and Blister Pack. (b) (4) The sponsor was notified of this deficiency and agreed to amend (b) (4) at the next printing. This is acceptable to the Agency.

Recommendation:

Adequate information has been provided to support the proposed changes. The supplement, therefore, is recommended for approval.

ONDQA-Biopharmaceutics Review:

The ONDQA-Biopharmaceutics Reviewer determined that the dissolution character of the reformulated PREMPRO™ 0.3 mg/1.5 mg tablet is comparable to the 0.45 mg/1.5 mg tablet. The biowaiver for the lower strength tablet, therefore, is justified, and granted.

The ONDQA-Biopharmaceutics Reviewer accepted the justification provided by the Sponsor on April 22, 2009 for the final MPA acceptance criteria shown below:

Time	% MPA Dissolved
30 minutes	(b) (4)
90 minutes	(b) (4)

DRUP Review of the Labeling Submitted with NDA 20-527/SCF-046:

The labeling submitted in NDA 20-527/SCF-046 complies with the last approved PREMPRO™/PREMPHASE® labeling, dated March 3, 2008, with the following exceptions:

(b) (4)

5 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

DRUP Comments and Recommendations:

The labeling submitted in NDA 20-527/SCF-046 incorporated changes in the DESCRIPTION, CLINICAL PHARMACOLOGY, and HOW SUPPLIED sections of the Physician Insert, and in the Patient Information leaflet under "What are the ingredients in PREMPRO and PREMPHASE?" Clinical Pharmacology and ONDQA concur with the recommend changes. The clinical reviewer recommends approval of the submitted labeling for NDA 20-527/SCF-046.

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
4/23/2009 12:23:41 PM
MEDICAL OFFICER

Shelley Slaughter
4/24/2009 02:06:48 PM
MEDICAL OFFICER
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020527/S-046

CHEMISTRY REVIEW(S)

CHEMIST REVIEW #2
OF **SUPPLEMENT**
Prior Approval

1. **ORGANIZATION**: ONDQA-DPE
2. **NDA NUMBER:** 20-527 / SCF 046

3. **SUPPLEMENT DATES:**
   Letter/Stamp Date: 25-Jun-2008
   Due Date: 25-Oct-2008
4. **AMENDMENTS:** 12-Sept-2008
   Responses to CR Ltr: 23-Dec-2008
   Action Date: 23-Apr-2009
   Amendment: 22-Apr-2009
5. **RECEIVED BY CHEMIST:** Aug 2008

6. **SPONSOR NAME AND ADDRESS**
   Wyeth Pharmaceuticals
   Philadelphia, PA

7. **SUPPLEMENT PROVIDES FOR:** reformulated Prempro 0.30 mg Conjugated Estrogens/ 1.5 medroxyprogesterone acetate tablets and 0.45 mg Conjugated Estrogens/ 1.5 medroxyprogesterone acetate tablets with changes in the drug product specification

8. **DRUG PRODUCT NAME:** Prempro
9. **NONPROPRIETARY NAME:** Conjugated estrogens/ medroxyprogesterone acetate tablets
10. **DRUG SUBSTANCES:** Conjugated estrogens/ medroxyprogesterone acetate

11. **DOSAGE FORM/ROUTE OF ADMIN:** tablet, oral
12. **STRENGTHS:** 0.3 mg conjugated estrogens (CE)/ 1.5 mg medroxyprogesterone acetate (MPA); 0.45 mg CE/ 1.5 mg MPA; 0.625 mg CE/ 2.5 mg MPA; 0.625 mg CE; 5.0 mg MPA

13. **INDICATION:** hormone replacement
14. **HOW DISPENSED:** Rx
15. **RELATED IND/NDA/DMF:** Premarin, 4-782, SCF 137, 141, and 142, for the approval of reformulated Premarin

16. **COMMENTS:**
    Chemistry review #2 evaluates the proposed blister pack, container label, and carton for reformulated Prempro tablets, provides the ONDQA/Biopharmaceutics reviewer evaluation of the deficiencies conveyed to the sponsor in the Complete Response letter, and provides the final acceptance criteria for the MPA dissolution test.

17. CONCLUSIONS AND RECOMMENDATIONS

Adequate information has been provided to support the proposed changes. The supplement, therefore, is recommended for approval.

18. REVIEWER NAME	**DATE COMPLETED**
J. Salemme, Ph.D., Chemistry reviewer, ONDQA-DPE	14-Apr-2009

OND-managed, G. Lyght , ONDQA-DPE PM: CT-Z
Reviewed: Dr. Hasmukh Patel, Branch Chief, ONDQA-DPE

7 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

Jean Salemme
4/22/2009 02:03:49 PM
CHEMIST

Hasmukh Patel
4/22/2009 03:27:00 PM
CHEMIST

CHEMIST REVIEW
OF **SUPPLEMENT**
Prior Approval

1. **ORGANIZATION**: ONDQA-DPE
2. **NDA NUMBER:** 20-527 / SCF 046

3. **SUPPLEMENT DATES:**
Letter/Stamp Date: 25-Jun-2008
Due Date: 25-Oct-2008
4. **AMENDMENT:** 12-Sept-2008
5. **RECEIVED BY CHEMIST:** Aug 2008

6. **SPONSOR NAME AND ADDRESS**
Wyeth Pharmaceuticals
Philadelphia, PA

7. **SUPPLEMENT PROVIDES FOR:** reformulated Prempro 0.30 mg Conjugated Estrogens/ 1.5 medroxyprogesterone acetate tablets and 0.45 mg Conjugated Estrogens/ 1.5 medroxyprogesterone acetate tablets with changes in the drug product specification

8. **DRUG PRODUCT NAME:** Prempro
9. **NONPROPRIETARY NAME:** Conjugated estrogens/ medroxyprogesterone acetate tablets
10. **DRUG SUBSTANCES:** Conjugated estrogens/ medroxyprogesterone acetate

11. **DOSAGE FORM/ROUTE OF ADMIN:** tablet, oral
12. **STRENGTHS:** 0.3 mg conjugated estrogens (CE)/ 1.5 mg medroxyprogesterone acetate (MPA); 0.45 mg CE/ 1.5 mg MPA; 0.625 mg CE/ 2.5 mg MPA; 0.625 mg CE; 5.0 mg MPA

13. **INDICATION:** hormone replacement
14. **HOW DISPENSED:** Rx
15. **RELATED IND/NDA/DMF:** Premarin, 4-782, SCF 137, 141, and 142, for the approval of reformulated Premarin

16. **COMMENTS:**
The drug product, Prempro, consists of a Premarin core coated with medroxyprogesterone acetate coating. Reformulated Premarin tablets were approved in Supplement 4-782 SCF 137, 141, and 142. This supplement proposes a reformulated Prempro, consisting of the reformulated Premarin [Conjugated Estrogens, (CE)] core and a medroxyprogesterone acetate (MPA)/polymer sugar coating, for the two lower Prempro strengths, 0.30 mg CE/ 1.5 mg MPA, and 0.45 mg CE/ 1.5 mg MPA. A BE study was conducted to establish BE between the approved 0.45 mg/1.5 mg tablets and the reformulated 0.45/1.5 mg tablets. The BE study is being evaluated by Clinical Biopharmaceutics reviewer Dr. D. Tran. A biowaiver for the 0.30 mg/1.5 mg reformulated Prempro was previously granted pending a demonstration of bioequivalence for the reformulated 0.45 mg/1.5 mg Prempro.

Dissolution data provided to support the equivalence of the 0.30 mg/ 1.5 mg to the 0.45 mg/ 1.5 mg reformulated Prempro are not adequate to support the equivalence of the two strengths.

The proposed dissolution method for MPA, dissolution media, and dissolution acceptance criteria are being reviewed by the ONDQA/ Biopharmaceutics reviewer, and deficiencies noted by the reviewer will be conveyed to the sponsor.

17. CONCLUSIONS AND RECOMMENDATIONS

The information provided in this supplement is not adequate to support the proposed changes.

Action Item: Send a Complete Response Letter with the following deficiencies:

- **To support the newly proposed dissolution method for the analysis of MPA, provide the study report to justify the use of apparatus, dissolution medium, pH, and agitation speed. Additionally, provide data to support that the method is discriminatory.**

- **Provide the raw dissolution data (with at least 12 individual dosage units and the percent coefficient of variation at the earlier time points) and dissolution profiles, with f2 calculations, in appropriate media and pH, to support equivalence of reformulated 0.30 mg Premarin/1.5 mg MPA to the reformulated 0.45 mg Premarin/1.5 mg batch MPA batch used in the BE study. Perform the f2 calculations according to the CDER Guidance, with use of not more than one data point past (b) (4) dissolved.**

- **Limited dissolution data provided in the supplement for the six batches, (average and range of dissolution values), do not support the proposed acceptance criterion of (b) (4) % medroxyprogesterone acetate at 30 minutes and (b) (4) % at 90 minutes. Provide additional data to support the proposed acceptance criteria for the 30 minute and 90 minute testpoints.**

18. REVIEWER NAME / DATE COMPLETED

J. Salemme, Ph.D., Chemistry reviewer, ONDQA-DPE — 22-Oct-2008

OND-managed, G. Lyght , ONDQA-DPE PM: CT-Z
Reviewed: Dr. Hasmukh Patel, Branch Chief, ONDQA-DPE

28 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

Jean Salemme
10/23/2008 03:05:02 PM
CHEMIST

Hasmukh Patel
10/23/2008 03:12:04 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020527/S-046

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDQA (Biopharmaceutics) Review

NDA:	20527(SCF046)
Submission Date:	12/23/208
Product:	Pempro [*Conjugated estrogens (*CE)/ Medroxyprogesterone acetate (MPA)]
Type of Submission:	Biowaiver and Dissolution Specification
Sponsor:	Wyeth
Reviewer:	Tapash K. Ghosh, Ph.D.

Background: The sponsor requested biowaiver for reformulated 0.3 mg/1.5 mg strength, which is the lower strength of the two reformulated strengths. OCP review has accepted the higher strength (0.45 mg/1.5 mg) BE comparison study. The previous biopharmaceutics review from ONDQA by Dr. John Duan (DFSed on 10/23/2008) raised some issues in the methodology aspects of dissolution method and recommended that the sponsor needed to address those issues before biowaiver could be granted. This review will examine the sponsor's response to those issues in light of granting biowaiver for the lower strength.

Recommendations:

- *Based on the information submitted, the reviewer agrees with the sponsor's justification of the in-vitro dissolution method and concurs that the in- vitro dissolution method appears to have adequate discriminatory power to identify formulation variables.*

- *Based on the data submitted by the sponsor, the similarity of the dissolution profiles and the f2 values, biowaiver can be granted for the reformulated lower strength (0.3 mg/1.5 mg).*

- *However, the reviewer proposes the following MPA dissolution specification limits for the 30-minute and 90-minute time points:*

Time (minutes)	% MPA Dissolved
30	(b) (4) %
90	(b) (4) %

- *Regarding the new in-vitro dissolution method, the [redacted] (b) (4) provided only the following minor editorial change:*

[redacted] (b) (4)

The method was not reviewed and approved by the Agency. Therefore, the sponsor's language "currently approved MPA dissolution method (L18623-045)" is not correct. It is assumed that the sponsor did not use the method (L18623-045) for quality control purposes for any batch of Pempro manufactured so far. The sponsor is required to clarify that.

In the future, it is expected that any change in the dissolution method specification be submitted in a prior approval supplement.

- *As there is no mention about the dissolution specification of conjugated estrogens (CEs) in this submission, it is assumed that there is no change in the following in vitro dissolution method (USP XXIV apparatus 2, 900mL water, 37°C, and 50 rpm) and specification for CE for both strengths as accepted by the sponsor on April 12, 2001:*

Time	**% estrone sulfate released** (b) (4)
2 hours	[redacted]
5 hours	
8 hours	

The sponsor is required to clarify that.

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT Initialed by Patrick Marroum, Ph. D. _____

The questions and the sponsor's responses are described below with comments from the reviewer wherever applied.

FDA Request # 1: *Provide a statement regarding which submission to the NDA provides the approved MPA dissolution method (L18623-045).*

Response: The Medroxyprogesterone acetate (MPA) dissolution method (L18623-045) for Prempro 0.3mg /1.5mg and 0.45mg /1.5mg was originally approved on March 12, 2003 (NDA 20-527/S-017) and June 4, 2003 (NDA 20-527/S-024) respectively. The currently approved MPA dissolution method (L18623-045) was filed in the 2007 Prempro NDA Annual Report on January 16, 2008. Method L18623-045 for MPA dissolution of Prempro 0.3 mg/1.5 mg and 0.45 mg/1.5 mg tablets was renamed STM-00000501 and is included in this submission.

Reviewer's Comment: Regarding the new in-vitro dissolution method, (b) (4) *provided only the following minor editorial change:*

(b) (4)

The method was not reviewed and approved by the Agency. Therefore, the sponsor's language "currently approved MPA dissolution method (L18623-045)" is not correct. It is assumed that the sponsor did not use the method (L18623-045) for quality control purposes for any batch of Pempro manufactured so far. The sponsor is required to clarify that.

FDA Request # 2: *Provide a side by side comparison of the proposed MPA dissolution method (L26403-009) and the approved MPA dissolution method (L18623-045).*

Response: A side by side comparison of the proposed MPA dissolution rnethod (L26403-009) and the approved MPA dissolution method (L18623-045) is provided in Table 2-1 below.

Table 2-1: Comparison of MPA Dissolution Methods

Method Parameter	Method L18623-045	Method L26403-009
Apparatus	Disintegration Apparatus	USP Apparatus 2
Agitation Rate	30 dips/minute	50 rpm
Medium	0.54% Sodium Lauryl Sulfate in Water	0.54% Sodium Lauryl Sulfate in Water
[redacted] (b) (4)		

FDA Request # 3: *To support the newly proposed MPA dissolution method, provide the study report to justify the use of the apparatus, dissolution medium, pH, and agitation speed. Additionally, provide supporting data that the method is discriminatory.*

Response:

Evaluation of in-vitro Dissolution Method Development:

Apparatus Evaluation: For the currently approved PREMPRO tablets, MPA dissolution is carried out using method L18623-045 which employs the disintegration apparatus as specified in the USP <701> with 0.54% sodium lauryl sulfate (SLS) as the medium. Initially, the development of the new formulation was supported by the disintegration apparatus but it was replaced with a conventional USP Apparatus 2 (paddles) method with the goal of developing a more biorelevant method. [redacted] (b) (4) was not considered as a viable option because the inherent stickiness of the [redacted] (b) (4) tablets would not be suitable for baskets. Therefore, further development work focused on Apparatus 2 while considering media, paddle speed, etc. to satisfy the method development goals.

Dissolution Medium Evaluation: Historically, MPA disintegration and dissolution data had been generated using 0.54% SLS (to enhance MPA's solubility) in water. Additional dissolution studies were carried out to evaluate the effect on MPA dissolution rate when modifications were made to the SLS solution concentration. Decreased SLS concentration in the dissolution media [redacted] (b) (4) was evaluated for the potential

to better differentiate [redacted] formulations *in vitro*. In addition to evaluating the effects of varying SLS concentrations, the addition of [redacted] to the SLS media was investigated. In effect, relatively low pH [redacted] and higher pH [redacted] were encompassed in the study. Based upon the more robust performance of media that did not contain [redacted] (and thus higher pH) and no overall enhanced discrimination with the addition of [redacted] it was deemed that the 0.54% SLS without [redacted] was appropriate for this method.

Agitation Speed Evaluation: As part of the MPA dissolution development work, an evaluation of various paddle speeds was completed to determine how agitation speed would affect the rate of MPA release. A dissolution time of 120 minutes was selected for being both practical for a laboratory setting as well as physiologically relevant since peak plasma levels are generally achieved in less than 2 hours. Batches formulated to have different release rates were evaluated at [redacted] 50 and [redacted] rpm to determine the agitation speed that could most effectively differentiate the various MPA formulas. While [redacted] rpm gave the best separation among formulations, overall release of MPA at 120 minutes was considered to be too low for the fast and medium release formulations. By utilizing 50 rpm, there was good separation between formulations and at 120 minutes, [redacted] was released from the dosage form for the medium and fast release formulations. Therefore, 50 rpm was selected as the optimum agitation speed.

Dissolution Discrimination: Dissolution method L26403-009 was used to monitor the MPA dissolution performance of six, full production-scale batches of 0.45 mg/1.5 mg Premarin/MPA tablets containing different levels of the [redacted] in the MPA-containing sugar coat. Three pivotal bioequivalence studies were conducted to identify which of these [redacted] formulations was bioequivalent to the currently marketed PREMPRO reference tablet batch. The summary pharmacokinetic and dissolution data are presented in Table 3-1 for these studies. The data indicate that the method not only discriminates between the different release profiles but that there is a rank order correlation between the release rate (and level of [redacted] and the bioavailability of MPA from these formulations. Relevant data in Table 3-1 are graphically displayed in Figure 3-10 to further illustrate the dissolution method's ability to discriminate among formulations as a function of [redacted] levels.

Table 3-1: Dissolution and Bioavailability Data for Reformulated 0.45 mg/ 1.5 mg Premarin/MPA Batches Evaluated in Pivotal Bioequivalence Studies

Clinical Batch	(b) (4)	Bioavailability Relative to PREMPRO Batch A50441 Mean % (90% CI)		Biostudy Protocol
		C_{max}	AUC (0-∞)	
2006B0182		145% (132-159)	111% (104-119)	0713E1-134-US
2006B0180		131% (120-144)	106% (99-114)	0713E1-134-US
2007B0009		110% (98-124)	91% (84-100)	0713E1-1142-US
2006B0013		98% (87-109)	83% (76-91)	0713E1-1142-US
2005B0324		92% (82-103)	83% (76-90)	0713E1-1142-US
2005B0132		84% (75-94)	75% (69-82)	0713E1-133-US

MPA Dissolution: Apparatus 2,0.9L 0.54% sodium lauryl sulfate in water, 37°C, 50 rpm.
Note: The replicate dissolution values are data obtained from multiple tests conducted during the time frame that the bioequivalence studies were conducted.

(b) (4)

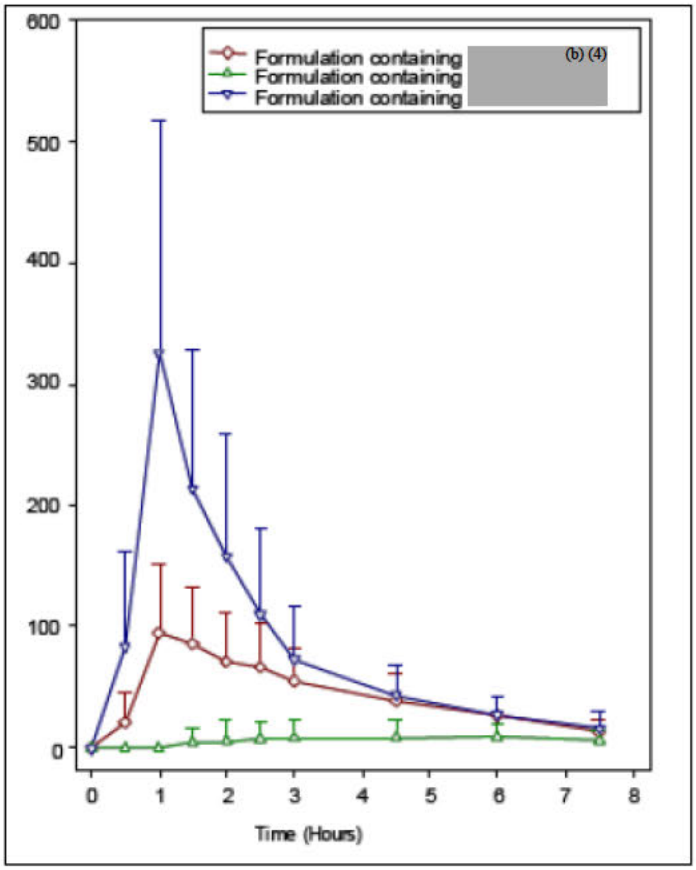
Reviewer's Comment: *Based on the information submitted, the reviewer agrees with the sponsor's justification of the method and concurs that the in- vitro dissolution method appears to have adequate discriminatory power to identify formulation variables as also evidenced by the following information.*

MPA is formulated as an immediate release drug with a time at which the maximum plasma concentration is achieved between 1 and 2 hours after oral absorption. To achieve MPA bioequivalence to the currently-approved PREMPRO tablets of these strengths, it was necessary to adjust the rate of release by incorporation of an appropriate concentration of the (b) (4) into the MPA-containing sugar/polymer coat. During product development and optimization of the MPA active coat formulation, the (b) (4) levels were varied to give an array of MPA dissolution profiles (fast, medium and slow) to help select a formulation for further evaluation. For example, prototype formulations of 0.45 mg/1.5 mg Premarin/MPA tablets, containing different concentrations of (b) (4) in the MPA-containing sugar/polymer coat, were evaluated in a pilot bioavailability study (Protocol 0713E1-131-US). Mean plasma

MPA concentration-time profiles are presented in Figure 3-1, which show that, the greater the concentration of (b) (4) the lower is the extent of MPA absorption.

The dissolution method was primarily developed and evaluated for its ability to robustly discriminate among such formulation variations. The *in vitro* MPA dissolution profiles of these prototype formulations, obtained using USP Apparatus 2 at 50 rpm with 900 mL of 0.54% sodium lauryl sulfate (SLS) in water at 37°C, parallel their respective *in vivo* plasma MPA concentration-time profiles, demonstrating a rank order relationship with (b) (4) content (Figure 3-2).

Figure 3-1: Premarin/MPA 0.45 mg/1.5 mg Pilot Biostudy (Protocol 0713E1-131-US) Mean (SD) Plasma MPA Levels (N=22) from Single Dose of 0.45 mg/1.5 mg Premarin/MPA Tablets

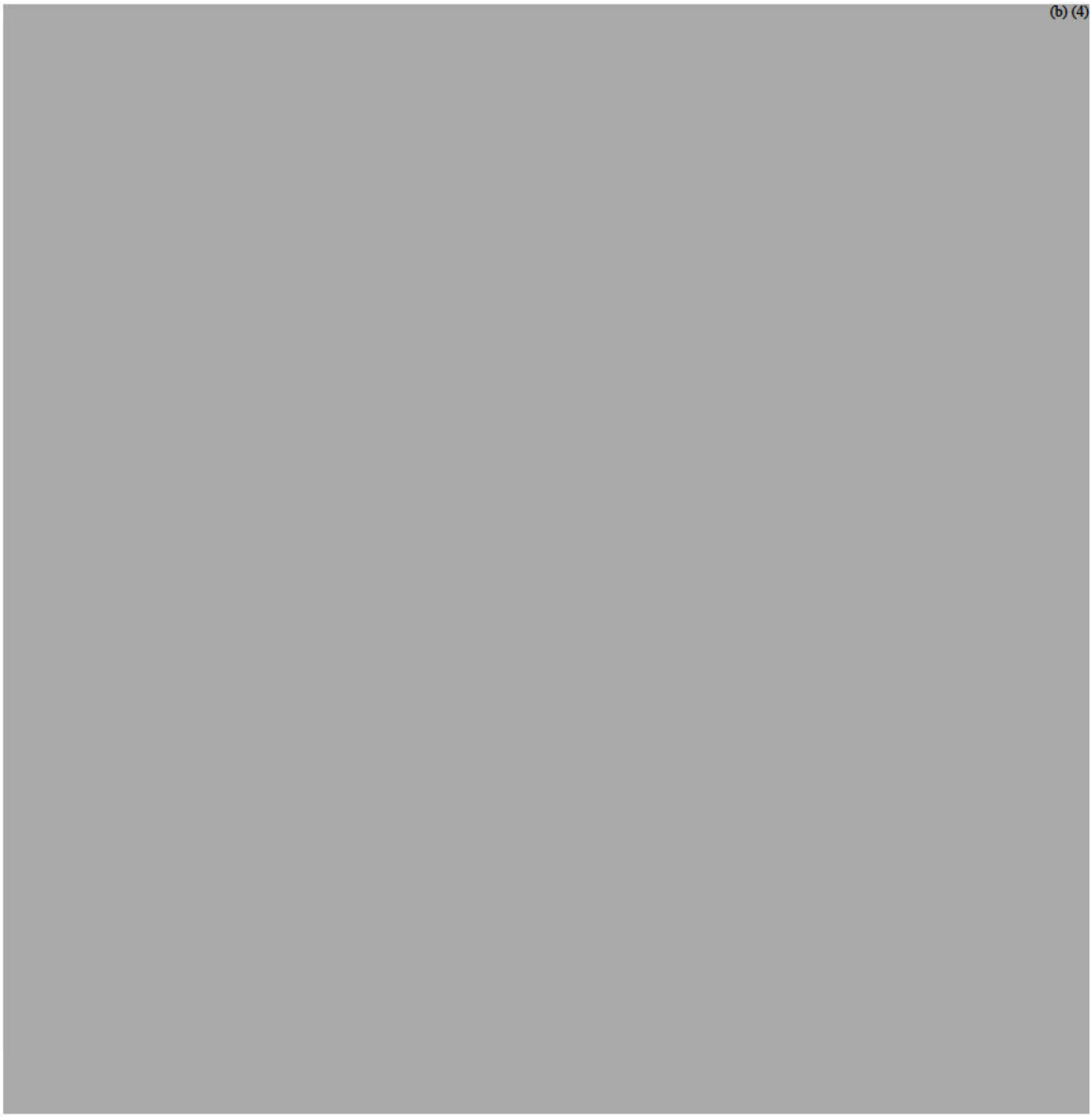


FDA Request # 4: *With a suitably justified dissolution method, provide (1) dissolution data for the reformulated batches and (2) dissolution profile comparisons between the reformulated 0.30 mg Premarin/1.5 mg MPA batches and the reformulated 0.45 mg Premarin/1.5 mg MPA batch used in the bioequivalence (BE) study. Provide the raw dissolution data (with at least 12 individual dosage units and the percent coefficient of variation at each time point) and dissolution profile comparisons with f2 calculations. Perform the f2 calculations according to the CDER Guidance with use of not more than one data point past* (b) (4).

Response:

Dissolution Data for Reformulated Batches: Raw dissolution data for the reformulated batches (N=12 tablets) are presented in Table 4-1 through Table 4-12. These data represent the six registration batches used in the reformulation: 2007B0006, 2007B0007, and 2007B0008 for the 0.3 mg Premarin/1.5 mg MPA and 2007B0009, 2007B0010 and 2007B0011 for the 0.45 mg Premarin/1.5 mg MPA. MPA dissolution was performed using Method L26403-009 and Conjugated Estrogens (CE) dissolution was performed using Method L26095-200.

Dissolution Comparison Profile of 0.3 mg Conjugated Estrogens/1.5 mg MPA: In addition to the data presented in Table 4-1 through Table 4-12, comparisons between the dissolution profiles are presented in Figure 4-1 and Figure 4-2 for the 0.3 mg Premarin/1.5 mg MPA Registration batches (Batches 2007B0006, 2007B0007, and 2007B0008) to the 0.45 mg Premarin/1.5 mg MPA used in the bioequivalence study (Batch 2007B0009). The methods used for the comparison are: L26403-009 for MPA and L26095-200 for Conjugated Estrogens.



5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page


(b) (4)

Taking into consideration only one time point past (b) (4) as per CDER Guidance, similarity factor (f2) calculations were performed using data at 15, 30, 45, 60 and 90 minutes for MPA and 1, 2, 3, 5 and 8 hours for Conjugated Estrogens. The f2(s) for the profiles from the three 0.3 mg Premarin/1.5 mg MPA registration batches compared to the reference 0.45 mg Premarin/1.5 mg MPA (Batch 2007B0009) were determined to be 90, 78, and 68 for MPA and 82, 95 and 95 for Conjugated Estrogens (CE) for Batches 2007B0006, 2007B0007, and 2007B0008, respectively. These results are greater than 50, the threshold at which dissolution profiles are considered to be similar.

f2 Values

Reference	Test	f2 (MPA)	f2 (CE)
0.45 mg Premarin/1.5 mg MPA (BE Batch 2007B0009)	0.30 mg Premarin/1.5 mg MPA (Batch 2007B0006)	**90**	**82**
0.45 mg Premarin/1.5 mg MPA (BE Batch 2007B0009)	0.30 mg Premarin/1.5 mg MPA (Batch 2007B0007)	**78**	**95**
0.45 mg Premarin/1.5 mg MPA (BE Batch 2007B0009)	0.30 mg Premarin/1.5 mg MPA (Batch 2007B0008)	**68**	**95**

Reviewer's Comment: *The reviewer's calculation of f2 values are similar to those reported by the sponsor.*

FDA Request # 5: *Limited dissolution data provided in the supplement for the six batches (average and range of dissolution values) do not support the proposed acceptance criterion of* (b) (4) *% MPA at 30 minutes and NLT* (b) (4) *% MPA at 90 minutes. Provide the raw dissolution data (with at least 12 individual dosage units and the percent coefficient of variation at each time point) to support the proposed acceptance criteria for the 30 minute and 90 minute time points.*

Response: MPA dissolution at 30 and 90 minutes from Premarin/MPA 0.3 mg /1.5 mg and 0.45 mg/1.5 mg registration stability data were statistically evaluated to assess the probabilities of passing USP <711> Acceptance Table 2 criteria for Level 1 and Level 2 based on various proposed specification limits. Stability samples were from six batches of two strengths: strength 0.3 mg/1.5 mg – batches 2007B0006, 2007B0007 and 2007B0008; strength 0.45 mg/1.5 mg – 2007B0009, 2007B0010 and 2007B0011. Samples from all batches except 2007B0009 were stored at 25.C/60%RH for up to six months. Samples from batch 2007B0009 were stored at 25.C/60%RH for up to twelve months and this batch was shown to be bioequivalent to the currently-approved PREMPRO product.

Based on the data analyses and simulation, the sponsor proposed the following MPA dissolution specification limits for the 30-minute and 90-minute time points:

Time (minutes)	**% MPA Dissolved**
30	(b) (4)
90	

The requirements are met if the specifications conform to USP <711> Table 2 criteria at the 30-minute and 90-minute time points. The 25°C/60%RH data used for this estimation are provided in Table 5-1 through Table 5-6 and include n=12 units for the initial test point and n=6 units for the remaining test points, with the exception of batch 2007B0011 at 9 months in blisters, which went to Stage 2. Included are individual values, average and coefficient of variation for each stability point. These data tables additionally include the individual dissolution and CV values for the 9 month stability data submitted to the FDA in September 2008.

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Reviewer's Comment: *Based on the data submitted by the sponsor, the reviewer proposes the following MPA dissolution specification limits for the 30-minute and 90-minute time points:*

Time (minutes)	**% MPA Dissolved**
30	(b) (4)
90	

Overall Conclusions:

- *Based on the information submitted, the reviewer agrees with the sponsor's justification of the in-vitro dissolution method and concurs that the in- vitro dissolution method appears to have adequate discriminatory power to identify formulation variables.*

- *Based on the data submitted by the sponsor, the similarity of the dissolution profiles and the f2 values, biowaiver can be granted for the reformulated lower strength (0.3 mg/1.5 mg).*

- *However, the reviewer proposes the following MPA dissolution specification limits for the 30-minute and 90-minute time points:*

Time (minutes)	% MPA Dissolved
30	(b) (4)
90	

- *Regarding the new in-vitro dissolution method, the update in the* (b) (4) *provided only the following minor editorial change:*

(b) (4)

The method was not reviewed and approved by the Agency. Therefore, the sponsor's language "currently approved MPA dissolution method (L18623-045)" is not correct. It is assumed that the sponsor did not use the method (L18623-045) for quality control purposes for any batch of Pempro manufactured so far. The sponsor is required to clarify that.

In the future, it is expected that any change in the dissolution method specification be submitted in a prior approval supplement.

- *As there is no mention about the dissolution specification of conjugated estrogens (CEs) in this submission, it is assumed that there is no change in the following in vitro dissolution method (USP XXIV apparatus 2, 900mL water, 37°C, and 50 rpm) and specification for CE for both strengths as accepted by the sponsor on April 12, 2001:*

Time	% estrone sulfate released
2 hours	(b) (4)
5 hours	
8 hours	

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

/s/

Tapash Ghosh
4/13/2009 03:14:33 PM
BIOPHARMACEUTICS

Patrick Marroum
4/13/2009 04:48:38 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 20-527/S-046	Submission Date(s): 6/25/2008, 10/20/2008, 12/23/2008
Brand Name	Prempro and Premphase
Generic Name	Conjugated estrogens/medroxyprogesterone acetate (CE/MPA)
Reviewer	Doanh Tran, Ph.D.
OCP Secondary Reviewer	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	Wyeth
Submission Type	Resubmission
Formulation; Strength(s)	Tablets; Prempro: 0.3 mg/1.5 mg (CE/MPA), 0.45 mg/1.5 mg, 0.625 mg/2.5 mg, and 0.625 mg/5 mg combination tablets. Premphase: 0.625 mg CE tablets and 0.625 mg/5 mg CE/MPA combination tablets
Indications	1. Treatment of moderate to severe vasomotor symptoms due to menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. 3. Prevention of postmenopausal osteoporosis.

Table of Contents

1 Executive Summary

In supplemental NDA 20-527/S-046, the sponsor proposed to market the new formulations of Prempro 0.45 mg/1.5 mg (conjugated estrogens (CE)/medroxyprogesterone acetate (MPA)) and Prempro 0.3 mg/1.5 mg tablets. The new formulation of Prempro 0.45 mg/1.5 mg tablets was supported by a bioequivalence study (Study 0713E1-1142-US) to the current approved formulation. The sponsor also sought a biowaiver for the new formulation of Prempro 0.3 mg/1.5 mg tablets.

The Clinical Pharmacology review of NDA 20-527/S-046 (DFS date, 10/23/2008) addressed the bioequivalence of Prempro 0.45 mg/1.5 mg tablets and the Office of New Drug Quality Assessment (ONDQA) addressed the biowaiver request.

The new formulation of Prempro 0.45 mg/1.5 mg was found to be bioequivalent to the currently approved formulation of the same tablet strength. However, data to support the long-term storage stability for MPA were not provided by the sponsor and the sponsor was requested in a Complete Response (CR) letter dated 12/15/2008 to provide the data for review.

The CR letter included the following Clinical Pharmacology deficiency:

> "Data to support the long-term stability of medroxyprogesterone acetate (MPA) in stored samples were not provided. Provide such data (i.e., sample stability study report) for review."

In this resubmission of NDA 20-527/S-046, the sponsor has provided evidence of long-term storage stability for MPA. Therefore, the sponsor has satisfied all outstanding Clinical Pharmacology issues as stated in the CR letter dated 12/15/2008.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds the Clinical Pharmacology section of NDA 20-527/S-046 acceptable.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The sponsor provided study report RPT-75623, which documented the long term stability of MPA in plasma. Two sets of MPA in sodium heparin plasma samples were made to assess long-term stability. The first set was prepared on 4/19/2005 and tested on 11/2/2005, i.e., following 197 days of storage. The second set was prepared on 5/11/2006 and tested on 11/14/2008, i.e., following 918 days of storage. Each set contained 6 replicates of each 15.0 pg/mL and 2000 pg/mL concentration levels. The concentration was measured using (b) (4) (also referred to as Wyeth report RPT-59600). This validated assay was previously reviewed (see Clinical Pharmacology review of NDA 20-527/S-046, DFS date, 10/23/2008). Table 1 shows the results.

Table 1: Measured Values of MPA in Human Plasma Stability Samples Stored at -80°C

	Concentration (pg/mL)	
Analysis Date	**02 Nov 2005[a]**	**14 Nov 2008[b]**
Days Since Preparation	**197**	**918**
	14.8	17.1
Low QC	14.1	17.1
15.0	14.4	16.9
	15.0	17.2
	17.2	16.8
	12.4	16.2
Mean	14.7	16.9
SD	1.55	0.366
CV (%)	10.5	2.17
Mean Bias (%)	-2.00	12.7
n	6	6
	1840	2080
High QC	2070	2140
2000	1690	2140
	2050	2130
	1940	2130
	2100	2150
Mean	1950	2130
SD	159	24.8
CV (%)	8.15	1.16
Mean Bias (%)	-2.50	6.50
n	6	6

a. All QCs prepared 19 Apr 2005.
b. All QCs prepared 11 May 2006.

The results indicate that MPA in sodium heparin plasma stored at -80 ºC was stable after 197 and 918 days. It should be noted that the concentrations of stability samples were compared to their theoretical concentrations instead of back-calculated concentration as measured on the first day of long-term stability. It is generally preferred that the concentrations of stability samples are compared to the mean of back-calculated values for the same standards on the first day of long-term stability. This is done to reduce confounding effects due standard sample preparation error.

There does not appear to be any specific bias with the set of samples on stability for 197 days. The calculated concentrations scattered about the theoretical mean concentration. There was a general upward bias for the second set of samples that was tested following 918 days in storage. This occurred at both high and low concentrations. Additionally, it would have been better to have aliquots of the sample standard samples tested on multiple occasions to confirm the long term stability. However, the totality of the data supports stability of MPA stored at -80 ºC for 918 days.

The sponsor reported that the maximum duration of study samples to remain frozen from clinical study start to last sample assayed were 33 days for bioavailability study 0713E1-132-US and 132 days for pivotal BE study 0713E1-1142-US. Therefore, the documented storage stability sufficiently covered the storage time intervals in these studies.

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

/s/

Doanh Tran
2/20/2009 03:14:02 PM
PHARMACOLOGIST

Myong-Jin Kim
2/20/2009 03:22:42 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 20-527/S-046	Submission Date(s): 6/25/2008, 10/20/2008
Brand Name	Prempro and Premphase
Generic Name	Conjugated estrogens/medroxyprogesterone acetate (CE/MPA)
Reviewers	Doanh Tran, Ph.D. (Clinical Pharmacology review except analytical methods) Chongwoo Yu, Ph.D. (Analytical methods review)
OCP secondary reviewer	Hae Young Ahn, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Reproductive and Urologic Products
Sponsor	Wyeth
Submission Type	Chemistry supplement
Formulation; Strength(s)	Tablets; Prempro: 0.3 mg/1.5 mg (CE/MPA), 0.45 mg/1.5 mg, 0.625 mg/2.5 mg, and 0.625 mg/5 mg combination tablets. Premphase: 0.625 mg CE tablets and 0.625 mg/5 mg CE/MPA combination tablets
Indications	1. Treatment of moderate to severe vasomotor symptoms due to menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. 3. Prevention of postmenopausal osteoporosis.

Table of Contents

1 Executive Summary

In this supplemental NDA (sNDA), the sponsor proposes to market new formulations of Prempro 0.45 mg/1.5 mg (conjugated estrogens (CE)/medroxyprogesterone acetate (MPA)) and Prempro 0.3 mg/1.5 mg tablets. The new formulation of Prempro 0.45 mg/1.5 mg tablets is supported by a bioequivalence study (Study 0713E1-1142-US) to the current approved formulation. The sponsor is seeking a biowaiver for the new formulation of Prempro 0.3 mg/1.5 mg tablets.

This review addresses the bioequivalence of Prempro 0.45 mg/1.5 mg tablets. The Office of New Drug Quality Assessment (ONDQA) will address the biowaiver request.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds the Clinical Pharmacology section of this supplement to NDA 20-527 not acceptable.

The results indicate that the new formulation of Prempro 0.45 mg/1.5 mg is bioequivalent to the current approved formulation of the same tablet strength. However, data to support the long-term storage stability for MPA were not provided by the sponsor. The sponsor should be requested to provide these data for review.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Background:

Currently, Wyeth markets CE/MPA tablets in several strengths (0.3/1.5 mg, 0.45/1.5 mg, 0.625/2.5 mg and 0.625/5.0 mg) as colored, branded, sugar coated tablets, consisting of Conjugated Estrogens, USP contained in (b) (4) covered by inert sugar coat, an active coat containing MPA, (b) (4)

(b) (4) The sponsor has developed a new formulations of CE 0.45 mg/MPA 1.5 mg and CE 0.3 mg/MPA 1.5 mg combination tablets.

The manufacture of the CE drug substance remains unchanged. However, it is incorporated into a (b) (4) as is used for the current market product. (b) (4) was modified extensively, including the addition of Eudragit NE 30 D, to obtain a suitable in vivo bioavailability profile.

Bioequivalence:
A pivotal bioequivalence study was performed in healthy, postmenopausal women to compare the rate and extent of absorption of estrogens and MPA from the new to-be-marketed tablet formulation with the currently marketed Prempro product. This study was a single-dose, crossover design in 72 healthy, postmenopausal women. Four (4) tablets of each CE 0.45 mg/MPA 1.5 mg formulation were administered.

The 90% confidence intervals for the CE 0.45 mg/MPA 1.5 mg new formulation met the criteria for bioequivalence to the current Prempro 0.45 mg/1.5 mg marketed product with respect to estrogens and MPA. The 90% CI of test/reference ratios of AUC and Cmax of the 4 primary moieties used for BE evaluation of conjugated estrogens (i.e., baseline-adjusted unconjugated estrone, baseline-adjusted total estrone, unconjugated equilin, and total equilin) and MPA were within 80 – 125% limits. Most other CE moieties tested were also within the required limits.

Fed bioequivalence:
In a letter to sponsor on 12/21/2006, the Office of Clinical Pharmacology granted a waiver of a fed BE study for all reformulated Premarin/MPA tablets. Therefore, the need for a fed BE study was not pursued in this review.

Bioanalytical:
Bioequivalence study 0713E1-1142-US used validated assays for CE moieties and MPA. However, data to support the long-term storage stability for MPA were not provided by the sponsor.

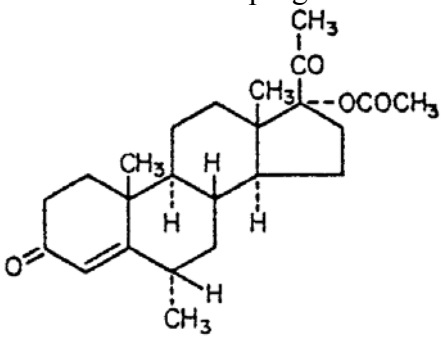
2 Question Based Review

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance?

The conjugated equine estrogens found in Prempro and Premphase 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. Its structural formula is:



2.2 General Clinical Pharmacology

The current product label indicates the following:

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.

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 doseproportional 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 (b) (4) followed by reabsorption. In postmenopausal women a significant proportion of the circulating estrogens (b) (4) as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens. Metabolism and elimination of MPA (b) (4) 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.

2.3 General Biopharmaceutics

Currently, Wyeth markets CE/MPA tablets in several strengths (0.3/1.5 mg, 0.45/1.5 mg, 0.625/2.5 mg and 0.625/5.0 mg) as colored, branded, sugar coated tablets, consisting of Conjugated Estrogens, USP contained in a (b) (4) See Appendix 4.3 for the composition of the current approved formulations for Prempro 0.3/1.5 mg and 0.45/1.5 mg tablets (taken from Chemistry review of NDA 20-527/SE1-024 by David Lin (DFS date 8/21/2002).

(b) (4) including the addition of Eudragit NE 30 D, to obtain a suitable in vivo bioavailability profile.

Several new formulations of CE/MPA tablets were developed and administered in pilot bioavailability and bioequivalence studies. For these formulations, (b) (4)

The reformulated Prempro 0.3 mg/1.5 mg and 0.45 mg/1.5 mg tablets contain the same conjugated estrogens 0.3 mg and 0.45 mg (b) (4) core tablet as approved in NDA 04-782 for Premarin 0.3 mg and Premarin 0.45 mg tablets and has an active medroxyprogesterone acetate in a sugar coat (b) (4) The formulations of the proposed new to-be-marketed Prempro 0.3 mg/1.5 mg and 0.45 mg/1.5 mg tablets are show in tables 1 and 2.

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

2.3.1 What bioavailability and bioequivalence data are available to support the new formulation of CE 0.45 mg/MPA 1.5 mg tablets?

The sponsor provided study reports to six bioavailability and bioequivalence studies (Table 3).

Table 3: Summary of bioavailability/bioequivalence studies for CE 0.45 mg/MPA 1.5 mg formulations

Protocol Number	Study Objective	CSR Number
0713E1-131-US	Bioavailability of 3 pilot formulations	57499
0713E1-132-US	Bioavailability of 4-tablet dose administration	59804
0713E1-133-US	Bioequivalence/Bioavailability of 4 pilot formulations	64703
0713E1-134-US	Bioequivalence of 2 test formulations	68899
0713E1-135-US	Bioavailability of 6 pilot formulations	65222
0713E1-1142-US	Bioequivalence of 3 test formulations	72630

Study 0713E1-1142-US was a pivotal bioequivalence study that included the proposed new to-be-marketed formulation. This study was reviewed and discussed in the next section. Other studies used prior pilot formulations and were not reviewed in details.

2.3.2 Is the proposed new to-be-marketed formulation of CE 0.45 mg/MPA 1.5 mg bioequivalent to the approved formulation?

The bioequivalence of the proposed new to-be-marketed formulation of CE 0.45 mg/MPA 1.5 mg (designated as Formulation A or Treatment A in study 0713E1-1142-US) to the approved Prempro 0.45 mg/1.5 mg formulation (designated as Treatment D) was evaluated in a single dose, crossover bioequivalence study under fasting condition in 72 postmenopausal women (Study 0713E1-1142-US, See Appendix 4.1). Due to assay limitations, the study administered 4 tablets of each formulation in order to obtain an extended PK profile for assessment of MPA bioavailability. A summary of results is presented below.

Table 4: Summary of pharmacokinetic data for Treatments A and D (Study 0713E1-1142-US)

	Treatment A				Treatment D			
Ligand	C_{max} (ng/mL)	t_{max} (h)	AUC (ng•h/mL)	$t_{½}$ (h)	C_{max} (ng/mL)	t_{max} (h)	AUC (ng•h/mL)	$t_{½}$ (h)
Total Estrone	5.39 ± 2.62[a]	7.9	119 ± 57	22.4	5.55 ± 2.11	8.9	131 ± 69	22.3
Total Estrone Adjusted for Baseline	5.22 ± 2.53	7.9	99.8 ± 46.9	15.1	5.38 ± 2.04	8.9	110 ± 53	16.3
Total Equilin	4.33 ± 1.80	6.5	73.8 ± 35.6	11.6	4.58 ± 1.61	7.9	78.4 ± 35.8	11.7
	C_{max} (pg/mL)	t_{max} (h)	AUC (pg•h/mL)	$t_{½}$ (h)	C_{max} (pg/mL)	t_{max} (h)	AUC (pg•h/mL)	$t_{½}$ (h)
Unconjugated Estrone	149 ± 52	8.9	6641 ± 2583	37.5	159 ± 54	10.1	6880 ± 3053	35.7
Unconjugated Estrone Adjusted for Baseline	130 ± 52	8.9	3799 ± 1800	21.2	139 ± 54	10.1	4199 ± 1973	21.7
Unconjugated Equilin	83 ± 32	8.3	1889 ± 750	15.9	86 ± 32	9.0	1932 ± 783	15.2
Medroxyprogesterone acetate	724 ± 475	2.0	4963 ± 3038	26.2	673 ± 487	2.7	5394 ± 3260	27.6

Protocol 0713E1-1142-US was the pivotal bioequivalence study and used a randomized cross-over, single Premarin 0.45 mg/MPA 1.5 mg dose design and involved 72 healthy postmenopausal women with a mean age of 58 years (range of 46 to 70 years).
Treatment A: 4 tablets of Premarin 0.45 mg/MPA 1.5 mg (test formulation A; Batch 2007B0009) administered orally.
Treatment D: 4 tablets of Prempro (reference Premarin 0.45 mg/MPA 1.5 mg; formulation D; Batch A50441) administered orally.
a. Mean ± standard deviation.

Table 5: Statistical results from the comparison of treatment A to Prempro presented as Mean Ratios (90% Confidence Intervals), Study 0713E1-1142-US.

Estrogens	C_{max}	AUC_t	AUC
Unconjugated			
Estrone	93 (88-99)	95 (91-99)	96 (91-100)
Estrone adjusted for baseline	92 (86-98)	91 (86 - 96)	91 (86-97)
Equilin	94 (89 - 100)	96 (90-102)	98 (93-105)
17β-Estradiol	94 (86-102)	95 (88-102)	92 (83-101)
17β-Estradiol adjusted for baseline	90 (82-98)	87 (79-95)	89 (82-97)
17β-Dihydroequilin	92 (87-98)	93 (88-99)	92 (88-98)
$\Delta^{8,9}$-DHES	99 (93 - 104)	102 (86 - 121)	N/A
17β-$\Delta^{8,9}$-DHESTR	96 (90 - 101)	95 (88 - 101)	95 (89 - 101)
Total			
Estrone	93 (87-99)	92 (87-96)	91 (86- 95)
Estrone adjusted for baseline	93 (87-99)	91 (86 - 96)	90 (85- 95)
Equilin	92 (86 - 98)	93 (88 - 98)	92 (88 - 97)
17β-Estradiol	93 (86- 100)	90 (84 - 97)	90 (84 - 97)
17β-Estradiol adjusted for baseline	93 (86 - 101)	90 (84 - 98)	88 (82 - 94)
17β Dihydroequilin	96 (90 - 102)	93 (88 - 99)	95 (90 - 100)
$\Delta^{8,9}$-DHES	98 (92-104)	95 (90 - 100)	95 (90 - 99)
17β-$\Delta^{8,9}$-DHESTR	95 (90- 101)	95 (89-100)	95 (90 - 101)
MPA	110 (98-124)	94 (86-102)	91 (84-100)

Abbreviations: DHES = dehydroestrone, DHESTR = dehydroestradiol, NA = Not Applicable.

The results indicated that the point estimates for the test/reference ratios for Treatment A and Prempro were generally less than 100% for conjugated estrogens moieties. However, the 90% CIs for Cmax, AUC0-t, and AUC0-inf test/reference ratios for treatments A and D were within 80% to 125% for all tested moieties of conjugated estrogens with the exception of baseline-adjusted 17β-estradiol AUC0-t. The lower limit of the 90% CI for this comparison was 78.55%, slightly under the required lower limit, and AUC0-inf was within the required range.

The point estimates for the test/reference ratios for treatments A and Prempro for the MPA component were 110%, 94%, and 91% for C_{max}, AUC0-t, and $AUC_{0-\infty}$, respectively. Evaluations of the individual concentration versus time profiles indicated high intersubject variability. The 90% CIs were all within 80 – 125% limits for MPA C_{max} and AUCs.

Based on these results, the proposed new to-be-marketed formulation of CE 0.45 mg/MPA 1.5 mg is considered to be bioequivalent to the approved Prempro 0.45 mg/1.5 mg formulation.

2.3.3 Was a fed bioequivalence study conducted?

In a letter to sponsor on 12/21/2006, the Office of Clinical Pharmacology granted a waiver of a fed BE study for all reformulated Premarin/MPA tablets. Therefore, the sponsor did not conduct a fed bioequivalence study and the need for such a study was not evaluated in this review.

2.4 Analytical Section

2.4.1 Did the Sponsor use validated bioanalytical assays to generate study data?

Yes. Gas chromatography - tandem mass spectrometry (GC-MS/MS) bioanalytical methods were developed, validated, and utilized in Studies 0713E1-132-US and 0713E1-1142-US for quantitation of unconjugated and total (unconjugated + conjugated) estrone, equilin, 17β-estradiol, 17β-dihydroequilin, $\Delta^{8,9}$-dehydroestrone, and 17β-$\Delta^{8,9}$-dehydroestradiol (Wyeth Research RPT-69055) as well as for quantitation of medroxyprogestrone (Wyeth Research RPT-69056) in human plasma samples.

Sample stability was adequately established for all analytes covering sample storage, extraction, and analysis time periods. It should be noted that at the Division's request, the Sponsor submitted an information amendment on October 20, 2008 via email (also submitted to document room on 10/20/2008) and stated that the sample storage stability of MPA has been established. However, no supporting documentation (i.e., study reports) was submitted and therefore, sample integrity remains as a concern. Sample extraction recovery was evaluated and found to be adequate and consistent for all analytes of interest. Intra-run and inter-run accuracy and precision for all analytes of interest have been assessed during method validation and found to be acceptable. Quality control (QC) samples were utilized during sample analytical runs in Studies 0713E1-132-US and 0713E1-1142-US to qualify the results as valid. Samples for two subjects were reanalyzed to demonstrate reproducibility of analytical results. Data demonstrate the reanalyzed samples were within pre-defined acceptance criteria except for unconjugated 17β-estradiol, unconjugated and total $\Delta^{8,9}$dehydroestrone. Since these analytes are not considered to be the primary determinants for bioequivalent assessment, this does not affect the validity of the bioanalytical methods.

In conclusion, the Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the bioanalytical methods used in this submission acceptable contingency on providing supporting documentation (i.e., study reports) of sample storage stability of MPA.

A summary of the bioanalytical methods is provided in the Appendix

6 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

4 Appendices

4.1 Individual Study Reviews

4.1.1 Bioequivalence Study 0713E1-1142-US

Review Note: The conjugated estrogen (CE) core for Prempro 0.45 mg/1.5 mg tablet is the same used in approved Premarin 0.45 mg tablets. The sponsor used the term Premarin to indicate the CE component in their report and this reviewer has used them interchangeably in this individual study review.

Title:
An Open-Label, Single-Dose, Randomized, 4-Period, Crossover, Bioequivalence Study of Three New Formulations of Premarin 0.45 mg/Medroxyprogesterone Acetate (MPA) 1.5 mg Compared With a Reference Formulation of Premarin 0.45 mg/MPA 1.5 mg (Prempro™) in Healthy Postmenopausal Women.

Objective:
To assess the bioequivalence of Premarin 0.45 mg/MPA 1.5 mg test formulations A, B, and C and the Premarin 0.45 mg/MPA 1.5 mg (Prempro) reference formulation D.

Methodology:
This was an open-label, single-dose, randomized, 4-period, 4-treatment, crossover, inpatient/outpatient study in healthy postmenopausal women (age range 46 – 70 years, mean age 57.6±5.44 years). Doses were administered after an overnight fast of at least 10 hours.

Number of patients/subjects:
Approximately 72 subjects were planned, 72 subjects were enrolled, and 72 subjects completed 1 or more treatments and were included in the pharmacokinetic analysis. Sixty seven (67) subjects completed all 4 treatments of the study.

Test product, dose and mode of administration, batch number:

- 4 tablets of oral Premarin 0.45 mg/MPA 1.5 mg tablet formulation A, batch number 2007B0009 (treatement A).
- 4 tablets of oral Premarin 0.45 mg/MPA 1.5 mg tablet formulation B, batch number 2006B0013 (treatement B).
- 4 tablets of oral Premarin 0.45 mg/MPA 1.5 mg tablet formulation C, batch number 2005B0324 (treatement C).

Reference therapy, dose and mode of administration, batch number:

- 4 tablets of oral Premarin 0.45 mg/MPA 1.5 mg marketed product reference tablet, batch number A50441 (treatment D).

Table 6: Study drug information

Drug Product	Strength (mg)	Dosage Form	Formulation Number (Stock Number)	Batch Number
Premarin/MPA test formulation A	0.45/1.5	Tablet	0932491B	2007B0009
Premarin/MPA test formulation B	0.45/1.5	Tablet	0932280B	2006B0013
Premarin/MPA test formulation C	0.45/1.5	Tablet	0932281B	2005B0324
Premarin/MPA (Prempro) reference formulation D	0.45/1.5	Tablet	9204997	A50441

Duration of treatment:
The clinical portion of the study was completed in approximately 4 months (4/20/2007 to 8/18/2007). Each subject participated in the study for approximately 14 weeks. This included a screening evaluation within 4 weeks before the study and four 6-day, 5-night inpatient periods with at least a 21-day washout interval between each test article administration.

Pharmacokinetics/pharmacodynamics and statistical methods:

Blood samples for CE moieties were obtained at -48, -24, -2, 1.5, 3, 4.5, 6, 7.5, 9, 10.5, 12, 14, 16, 24, 32, 40, 48, 60, 72 hours. Blood samples for MPA were obtained at -2, 0.5, 1, 2, 2.5, 3, 4.5, 6, 7.5, 9, 10.5, 12, 14, 16, 24, 32, 40, 48, 60, 72 hours.

Plasma concentrations were determined for MPA, unconjugated and total (unconjugated plus conjugated) estrone, equilin, 17β-estradiol, 17β-dihydroequilin, Δ8,9-dehydroestrone, and 17β-Δ8,9-dehydroestradiol after administration of each formulation. Baseline-adjusted estrone and 17β-estradiol concentrations were calculated by taking the average of the 3 baseline samples (hours -48, -24, and -2) and then subtracting this amount from each postdose sample. For baseline-adjusted analyses, time 0 was assigned a value of 0.

The plasma concentrations for each analyte were tabulated by nominal sample time and treatment. Concentrations below the limit of quantitation (BLQ) of the assay were reported as 0.

The pharmacokinetic parameters AUC0-t, AUC0-inf, Kel, t½, Cmax, and tmax were calculated from the plasma concentration-time data for MPA and unconjugated and total (unconjugated plus conjugated) estrone, equilin, 17β-estradiol, 17β-dihydroequilin, Δ8,9-dehydroestrone, and 17β-Δ8,9-dehydroestradiol for each treatment using noncompartmental methods. Pharmacokinetic parameters for estrone and 17β-estradiol (unconjugated and total) were also determined after adjustment for baseline concentrations.

A linear mixed-effects model was applied to the natural logarithm (ln)-transformed pharmacokinetic parameters AUC0-t, AUC0-inf, and Cmax using PROC MIXED

procedure in SAS. The linear mixed-effects model included sequence, treatment, and period as fixed effects and subject within sequence as the random effect.

The two 1-sided hypotheses were tested at the 5% level for AUC0-inf, AUC0-t, and Cmax by constructing 90% confidence intervals (CI) for the ratio of the test and reference means for each analyte. The 90% CI were obtained from the antilogs of the lower and upper bounds of the 90% CI for the differences in the least-squares means (LSM) of the ln-transformed data. Bioequivalence with respect to AUC0-inf, AUC0-t, and Cmax was concluded if the 90% CI of the ratios of the test and reference means fell within the range of 80% to 125%.

Analytical methods:

- Plasma unconjugated and total estrogens and MPA were analyzed using validated GC/MS/MS methods.

Pharmacokinetics results:

Formulation A is considered to be bioequivalent to Prempro. Comparisons of AUC and Cmax of the 4 primary CE components (baseline-adjusted unconjugated estrone, baseline-adjusted total estrone, unconjugated equilin, and total equilin) and MPA were within 80 – 125% limits. Most others CE component tested were also within the required limits. A summary of overall statistical comparisons are presented below.

Table 7: Statistical results from the comparison of treatment A to Prempro

Geometric Mean Ratio (90% CI) for Formulation A Versus Prempro

Analyte	C_{max}	AUC_{0-t}	AUC_{0-inf}
Unconjugated estrone	93.02 (87.56 - 98.82)	94.62 (90.73 - 98.68)	95.77 (91.31 - 100.45)
BA unconjugated estrone	91.66 (85.78 - 97.96)	91.10 (86.15 - 96.35)	91.12 (85.88 - 96.69)
Unconjugated equilin	94.37 (89.07 - 99.98)	95.56 (89.84 - 101.64)	98.48 (92.80 - 104.51)
Unconjugated 17β-estradiol	93.55 (85.93 - 101.86)	94.70 (88.27 - 101.60)	91.92 (83.34 - 101.38)
BA unconjugated 17β-estradiol	89.84 (82.24 - 98.14)	86.60 (78.55 - 95.47)	89.16 (81.90 - 97.07)
Unconjugated 17β-dihydroequilin	92.27 (87.30 - 97.52)	93.29 (88.01 - 98.89)	92.49 (87.62 - 97.64)
Unconjugated $\Delta^{8,9}$-dehydroestrone	98.67 (93.36 - 104.28)	102.08 (86.36 - 120.67)	.
Unconjugated 17β-$\Delta^{8,9}$-dehydroestradiol	95.82 (90.48 - 101.48)	94.52 (88.33 - 101.15)	94.60 (88.59 - 101.02)
Total estrone	92.79 (86.93 - 99.03)	91.59 (87.20 - 96.21)	90.82 (86.49 - 95.37)
BA total estrone	92.59 (86.62 - 98.97)	91.12 86.27 - 96.23)	90.06 (85.28 - 95.11)
Total equilin	91.72 (86.18 - 97.61)	92.54 (87.78 - 97.55)	92.39 (87.68 - 97.35)
Total 17β-estradiol	92.80 (85.78 - 100.38)	90.01 (83.85 - 96.62)	90.23 (83.83 - 97.13)
BA total 17β-estradiol	92.97 (85.83 - 100.71)	90.38 (83.77 - 97.51)	88.02 (82.16 - 94.30)
Total 17β-dihydroequilin	95.63 (89.75 - 101.88)	93.37 (88.45 - 98.56)	95.01 (90.15 - 100.13)
Total $\Delta^{8,9}$-dehydroestrone	97.74 (91.76 - 104.11)	94.67 (90.07 - 99.50)	94.53 (90.08 - 99.21)
Total 17β-$\Delta^{8,9}$-dehydroestradiol	95.27 (90.08 - 100.77)	94.60 (89.40 - 100.10)	95.31 (90.30 - 100.60)
MPA	110.26 (98.42 - 123.53)	93.85 (85.95 - 102.48)	91.21 (83.54 - 99.59)

BA = baseline-adjusted.

The point estimates for the test/reference ratios for treatments A and Prempro were generally less than 100% for conjugated estrogens components. However, the 90% CIs for Cmax, AUC0-t, and AUC0-inf test/reference ratios for treatments A and D were within 80% to 125% for all tested components of conjugated estrogens with the exception

of baseline-adjusted 17β-estradiol AUC0-t. The lower limit of the 90% CI for this comparison was 78.55%, just slightly under the required lower limit, and AUC0-inf was within the required range.

The point estimates for the test/reference ratios for treatments A and Prempro for MPA component were 110%, 94%, and 91% for C_{max}, AUC0-t, and $AUC_{0-\infty}$, respectively. The 90% CIs were all within 80 – 125% limits for MPA C_{max} and AUCs.

Treatments B and C versus Treatment D: The 90% CIs for estrone and equilin Cmax, AUC0-t, and $AUC_{0-\infty}$ test/reference ratios for treatments B and C vs treatment D were within 80% to 125%. The 90% CIs for estrogens 17β-estradiol, 17β-dihydroequilin, Δ8,9-dehydroestrone, and 17β-Δ8,9-dehydroestradiol were also within 80% to 125% with the exception of unconjugated Δ8,9-dehydroestrone AUC0-t (90% CI upper limit of approximately 150%). Most of the unconjugated Δ8,9-dehydroestrone concentrations were below the limit quantification of the assay and AUC0-inf could not be estimated. The sponsor asserted that the accuracy of estimations of AUC0-t for this analyte is questionable. The 90% CIs for MPA AUC0-t and $AUC_{0-\infty}$ test/reference ratios were not within 80% to 125% for the comparison of treatment B or C to treatment D. Geometric mean MPA AUCs for treatments B and C were approximately 17% lower than the reference treatment D.

Details PK results:

1. **Unconjugated estrone**

Figure 1: Mean (SD) plasma unconjugated estrone concentration versus time

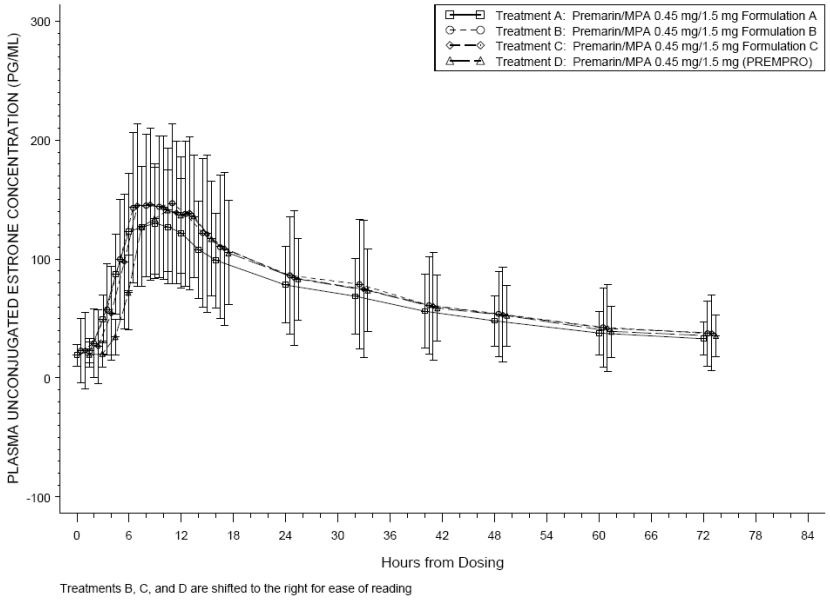


Table 8: Summary of the Pharmacokinetic Parameters of Plasma Unconjugated Estrone

Pharmacokinetic Parameters	Treatment A Arithmetic Mean	SD	Treatment B Arithmetic Mean	SD	Treatment C Arithmetic Mean	SD	Treatment D Arithmetic Mean	SD
C_{max} (pg/mL)	149	51.9	168	71.0	173	83.3	159	54.4
t_{max} (hr)	8.91	3.09	9.21	3.84	9.10	3.21	10.1	5.20
AUC_{0-t} (pg•hr/mL)	4674.15	1710.47	5267.58	2942.42	5169.72	3152.60	4920.15	1900.75
AUC_{0-inf} (pg•hr/mL)	6640.95	2583.06	7297.95	4577.82	7541.04	5589.05	6880.10	3053.28
$t_{½}$ (hr)	37.5	13.3	38.2	15.8	38.3	16.4	35.7	11.3
K_{el} (1/hr)	0.0204	0.00609	0.0205	0.00641	0.0206	0.00659	0.0212	0.00666
$ln(C_{max})$	4.949	0.3389	5.053	0.3646	5.068	0.4024	5.010	0.3501
$ln(AUC_{0-t})$	8.384	0.3736	8.473	0.4169	8.456	0.4070	8.430	0.3861
$ln(AUC_{0-inf})$	8.730	0.3836	8.791	0.4181	8.794	0.4736	8.753	0.4102

K_{el} = terminal-phase disposition rate constant; ln = natural logarithm.
Treatment A = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation A.
Treatment B = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation B.
Treatment C = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation C.
Treatment D = a single dose of Premarin 0.45 mg/MPA 1.5 mg (Prempro).

Table 9: Summary of Statistical Comparisons for Unconjugated Estrone Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment B vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment C vs Treatment D % Mean Ratio[a]	90% CI[b]
C_{max}	93.02	87.56 - 98.82	103.26	97.20 - 109.70	105.93	99.70 - 112.54
AUC_{0-t}	94.62	90.73 - 98.68	102.77	98.54 - 107.18	102.64	98.42 - 107.04
AUC_{0-inf}	95.77	91.31 - 100.45	102.75	98.03 - 107.71	104.17	99.41 - 109.15

2. **Baseline-Adjusted Unconjugated Estrone*****

Figure 2: Mean (SD) Baseline-Adjusted Plasma Unconjugated Estrone Concentrations Versus Time

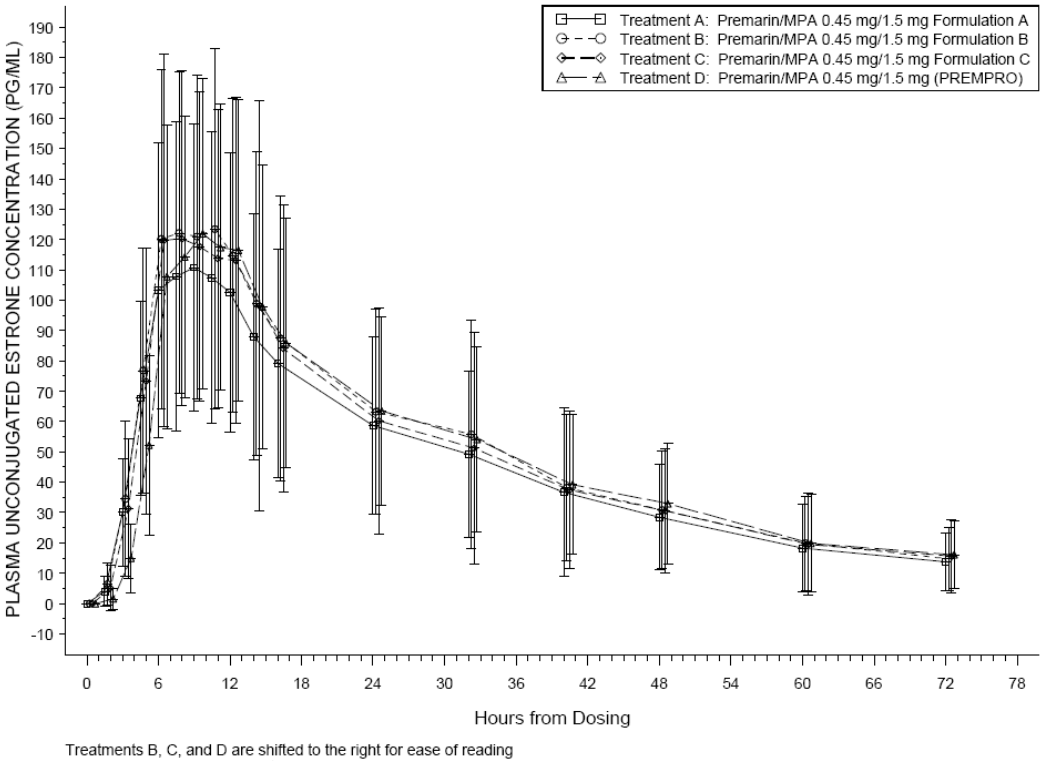


Table 10: Summary of Baseline-Adjusted Unconjugated Estrone Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A Arithmetic Mean	SD	Treatment B Arithmetic Mean	SD	Treatment C Arithmetic Mean	SD	Treatment D Arithmetic Mean	SD
C_{max} (pg/mL)	130	51.8	145	62.3	151	73.5	139	53.7
t_{max} (hr)	8.91	3.09	9.21	3.84	9.10	3.21	10.1	5.20
AUC_{0-t} (pg•hr/mL)	3257.73	1491.53	3606.14	1773.06	3580.05	1744.81	3507.82	1604.58
AUC_{0-inf} (pg•hr/mL)	3799.22	1799.67	4135.41	2116.52	4269.01	2337.93	4198.74	1973.14
$t_{½}$ (hr)	21.2	7.46	21.2	9.78	21.8	11.8	21.7	9.00
K_{el} (1/hr)	0.0368	0.0135	0.0381	0.0142	0.0406	0.0269	0.0369	0.0152
$ln(C_{max})$	4.787	0.4048	4.893	0.4084	4.918	0.4454	4.862	0.4016
$ln(AUC_{0-t})$	7.958	0.5699	8.061	0.5503	8.069	0.5075	8.047	0.5118
$ln(AUC_{0-inf})$	8.122	0.5191	8.191	0.5594	8.233	0.5149	8.229	0.4939

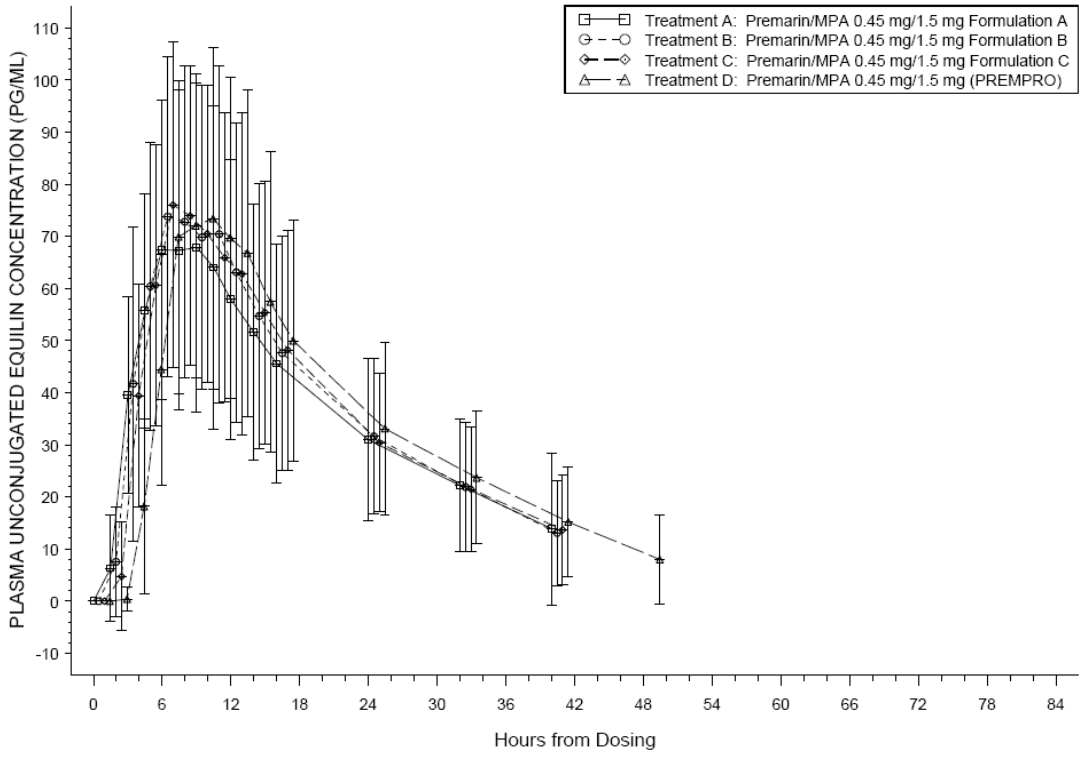
K_{el} = terminal-phase disposition rate constant; ln = natural logarithm.
Treatment A = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation A.
Treatment B = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation B.
Treatment C = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation C.
Treatment D = a single dose of Premarin 0.45 mg/MPA 1.5 mg (Prempro).

Table 11: Summary of Statistical Comparisons for Baseline-Adjusted Unconjugated Estrone Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment B vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment C vs Treatment D % Mean Ratio[a]	90% CI[b]
C_{max}	91.66	85.78 - 97.96	101.94	95.40 - 108.94	105.78	98.98 - 113.04
AUC_{0-t}	91.10	86.15 - 96.35	99.81	94.38 - 105.55	102.29	96.72 - 108.17
AUC_{0-inf}	91.12	85.88 - 96.69	98.12	92.51 - 104.08	102.56	96.66 - 108.82

3. **Unconjugated Equilin*****

Figure 3: Mean (SD) Plasma Unconjugated Equilin Concentrations Versus Time



Treatments B, C, and D are shifted to the right for ease of reading

Table 12: Summary of Unconjugated Equilin Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A Arithmetic Mean	SD	Treatment B Arithmetic Mean	SD	Treatment C Arithmetic Mean	SD	Treatment D Arithmetic Mean	SD
C_{max} (pg/mL)	83.1	31.9	87.9	34.4	88.0	32.4	86.1	32.2
t_{max} (hr)	8.27	3.96	8.09	4.45	8.00	4.69	9.03	3.97
AUC_{0-t} (pg•hr/mL)	1541.37	721.678	1581.06	704.286	1576.56	677.021	1596.81	730.880
AUC_{0-inf} (pg•hr/mL)	1889.04	750.094	1893.86	741.004	1868.23	725.983	1931.89	783.116
$t_{½}$ (hr)	15.9	7.06	14.2	5.54	14.3	5.30	15.2	6.45
K_{el} (1/hr)	0.0518	0.0224	0.0551	0.0193	0.0564	0.0277	0.0561	0.0319
$ln(C_{max})$	4.341	0.4141	4.396	0.4158	4.407	0.3890	4.383	0.3934
$ln(AUC_{0-t})$	7.219	0.5253	7.262	0.4842	7.278	0.4243	7.254	0.5348
$ln(AUC_{0-inf})$	7.460	0.4282	7.465	0.4246	7.462	0.3863	7.467	0.4903

K_{el} = terminal-phase disposition rate constant; ln = natural logarithm.
Treatment A = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation A.
Treatment B = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation B.
Treatment C = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation C.
Treatment D = a single dose of Premarin 0.45 mg/MPA 1.5 mg (Prempro).

Table 13: Summary of Statistical Comparisons for Unconjugated Equilin Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment B vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment C vs Treatment D % Mean Ratio[a]	90% CI[b]
C_{max}	94.37	89.07 - 99.98	99.60	94.02 - 105.52	102.46	96.71 - 108.55
AUC_{0-t}	95.56	89.84 - 101.64	99.02	93.09 - 105.32	102.35	96.23 - 108.86
AUC_{0-inf}	98.48	92.80 - 104.51	97.70	92.04 - 103.70	99.97	94.19 - 106.11

4. **Unconjugated 17β-Estradiol**

Figure 4: Mean (SD) unconjugated 17β-Estradiol concentrations versus time

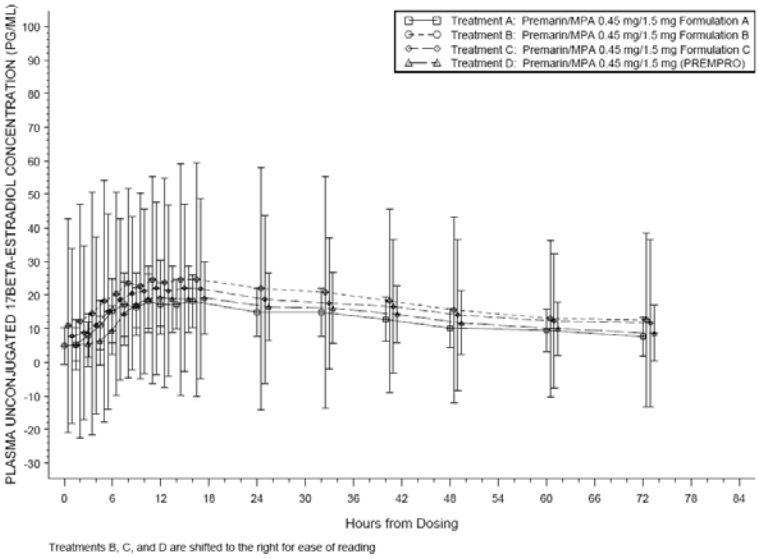


Table 14: Summary of Unconjugated 17β-Estradiol Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A Arithmetic Mean	SD	Treatment B Arithmetic Mean	SD	Treatment C Arithmetic Mean	SD	Treatment D Arithmetic Mean	SD
C_{max} (pg/mL)	22.0	10.1	29.6	38.2	29.6	37.4	23.7	11.3
t_{max} (hr)	12.8	8.33	13.2	7.39	15.6	11.9	14.6	8.94
AUC_{0-t} (pg•hr/mL)	897.510	415.058	1303.74	2121.63	1147.89	1560.33	972.168	612.583
AUC_{0-inf} (pg•hr/mL)	1303.39	579.295	2218.77	4449.47	2299.33	5459.45	1735.64	2229.71
$t_{½}$ (hr)	40.7	17.5	42.5	24.4	50.0	45.4	42.6	21.9
K_{el} (1/hr)	0.0198	0.00776	0.0207	0.0103	0.0196	0.0106	0.0190	0.00716
$ln(C_{max})$	3.022	0.3561	3.152	0.5285	3.145	0.5378	3.079	0.3982
$ln(AUC_{0-t})$	6.713	0.4098	6.839	0.6196	6.786	0.5898	6.759	0.4673
$ln(AUC_{0-inf})$	7.083	0.4283	7.243	0.7153	7.240	0.7537	7.219	0.5615

K_{el} = terminal-phase disposition rate constant; ln = natural logarithm.
Treatment A = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation A.
Treatment B = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation B.
Treatment C = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation C.
Treatment D = a single dose of Premarin 0.45 mg/MPA 1.5 mg (Prempro).

Table 15: Summary of Statistical Comparisons for Unconjugated 17β-Estradiol Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment B vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment C vs Treatment D % Mean Ratio[a]	90% CI[b]
C_{max}	93.55	85.93 - 101.86	106.83	98.12 - 116.31	106.84	98.12 - 116.34
AUC_{0-t}	94.70	88.27 - 101.60	107.30	100.01 - 115.11	102.67	95.70 - 110.15
AUC_{0-inf}	91.92	83.34 - 101.38	106.07	96.32 - 116.81	104.40	94.90 - 114.86

5. **Baseline-Adjusted Unconjugated 17β-Estradiol**

Figure 5: Mean (SD) baseline-adjusted plasma unconjugated 17β-Estradiol concentration versus time

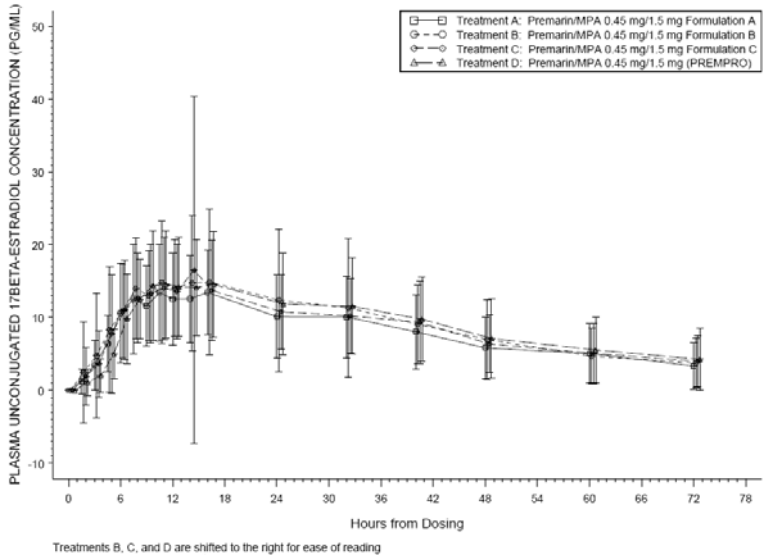


Table 16: Summary of Baseline-Adjusted Unconjugated 17β-Estradiol Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A Arithmetic Mean	SD	Treatment B Arithmetic Mean	SD	Treatment C Arithmetic Mean	SD	Treatment D Arithmetic Mean	SD
C_{max} (pg/mL)	17.3	7.59	19.6	11.7	21.6	24.0	18.8	8.13
t_{max} (hr)	12.8	8.33	13.4	7.31	15.6	11.9	14.7	8.97
AUC_{0-t} (pg•hr/mL)	557.971	285.142	627.004	319.532	619.639	261.360	633.855	332.816
AUC_{0-inf} (pg•hr/mL)	753.677	418.508	804.538	387.364	816.285	349.192	826.829	413.749
$t_{½}$ (hr)	27.0	11.9	26.2	15.3	26.6	13.4	25.9	9.71
K_{el} (1/hr)	0.0306	0.0132	0.0341	0.0180	0.0331	0.0178	0.0315	0.0146
$ln(C_{max})$	2.767	0.4003	2.898	0.3963	2.901	0.4765	2.870	0.4046
$ln(AUC_{0-t})$	6.199	0.5213	6.342	0.4972	6.301	0.6218	6.354	0.4776
$ln(AUC_{0-inf})$	6.493	0.5244	6.581	0.4854	6.616	0.4377	6.615	0.4526

K_{el} = terminal-phase disposition rate constant; ln = natural logarithm.
Treatment A = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation A.
Treatment B = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation B.
Treatment C = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation C.
Treatment D = a single dose of Premarin 0.45 mg/MPA 1.5 mg (Prempro).

Table 17: Summary of Statistical Comparisons for Baseline-Adjusted Unconjugated 17β-Estradiol Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment B vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment C vs Treatment D % Mean Ratio[a]	90% CI[b]
C_{max}	89.84	82.24 - 98.14	102.41	93.73 - 111.90	103.54	94.76 - 113.12
AUC_{0-t}	86.60	78.55 - 95.47	98.10	88.96 - 108.17	96.15	87.20 - 106.01
AUC_{0-inf}	89.16	81.90 - 97.07	92.91	85.31 - 101.17	101.80	93.47 - 110.88

6. **Unconjugated 17β-Dihydroequilin**

Figure 6: Mean (SD) plasma Unconjugated 17β-Dihydroequilin concentration versus time

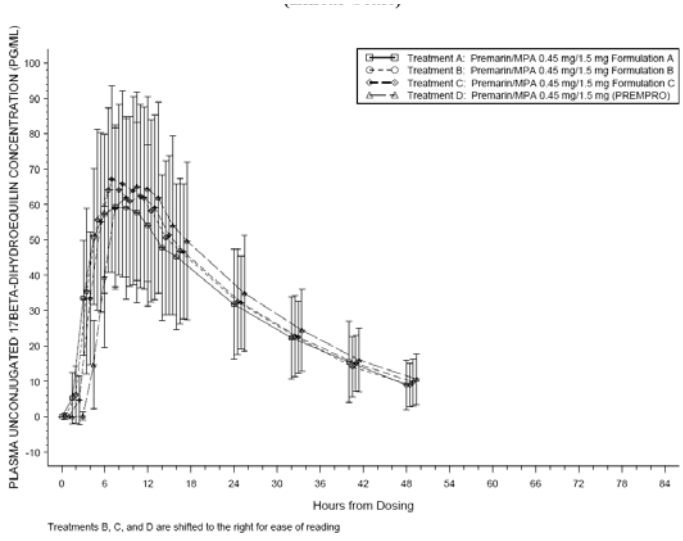


Table 18: Summary of Unconjugated 17β-Dihydroequilin Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A Arithmetic Mean	SD	Treatment B Arithmetic Mean	SD	Treatment C Arithmetic Mean	SD	Treatment D Arithmetic Mean	SD
C_{max} (pg/mL)	71.4	25.2	75.0	26.5	79.4	28.2	76.1	26.5
t_{max} (hr)	8.22	4.11	8.51	4.87	8.32	4.90	9.57	4.47
AUC_{0-t} (pg•hr/mL)	1544.72	658.042	1600.18	646.543	1625.13	583.558	1637.47	680.645
AUC_{0-inf} (pg•hr/mL)	1715.64	681.803	1761.38	651.148	1790.29	599.590	1820.17	687.413
$t_{½}$ (hr)	13.6	4.98	14.2	5.32	14.5	6.08	14.8	6.59
K_{el} (1/hr)	0.0560	0.0162	0.0538	0.0150	0.0542	0.0199	0.0534	0.0216
$ln(C_{max})$	4.201	0.3797	4.251	0.3817	4.309	0.3715	4.269	0.3661
$ln(AUC_{0-t})$	7.246	0.4643	7.292	0.4367	7.323	0.3943	7.306	0.4617
$ln(AUC_{0-inf})$	7.364	0.4300	7.405	0.3828	7.430	0.3624	7.431	0.4131

K_{el} = terminal-phase disposition rate constant; ln = natural logarithm.
Treatment A = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation A.
Treatment B = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation B.
Treatment C = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation C.
Treatment D = a single dose of Premarin 0.45 mg/MPA 1.5 mg (Prempro).

Table 19: Summary of Statistical Comparisons for Unconjugated 17β-Dihydroequilin Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment B vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment C vs Treatment D % Mean Ratio[a]	90% CI[b]
C_{max}	92.27	87.30 - 97.52	97.03	91.80 - 102.55	104.22	98.61 - 110.15
AUC_{0-t}	93.29	88.01 - 98.89	97.30	91.79 - 103.14	101.70	95.95 - 107.80
AUC_{0-inf}	92.49	87.62 - 97.64	96.92	91.84 - 102.29	100.47	95.19 - 106.03

7. **Unconjugated Δ8,9-Dehydroestrone**

Figure 7: Mean (SD) plasma Unconjugated Δ8,9-Dehydroestrone concentration versus time

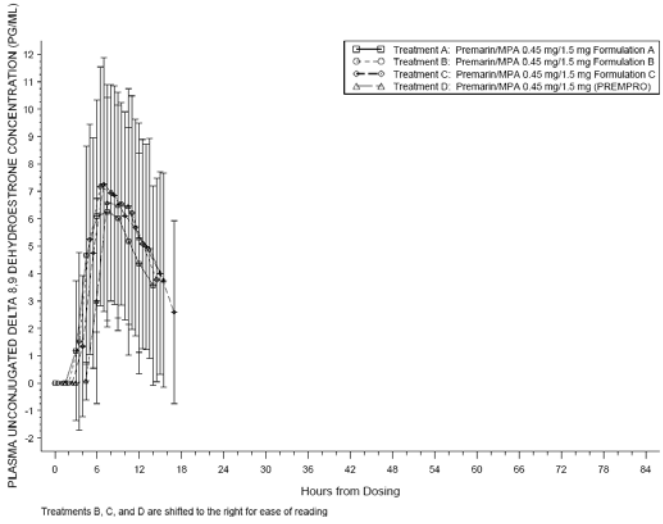


Table 20: Summary of Unconjugated Δ8,9-Dehydroestrone Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A Arithmetic Mean	SD	Treatment B Arithmetic Mean	SD	Treatment C Arithmetic Mean	SD	Treatment D Arithmetic Mean	SD
C_{max} (pg/mL)	8.14	3.98	9.02	3.90	8.67	4.06	8.42	3.87
t_{max} (hr)	7.88	2.65	7.38	2.39	7.51	2.16	7.87	1.99
AUC_{0-t} (pg•hr/mL)	63.0520	51.3343	75.7786	59.0316	69.9204	50.0748	65.9165	55.0734
AUC_{0-inf} (pg•hr/mL)	.	.	.	.	.	.	.	.
$t_{½}$ (hr)	.	.	.	.	.	.	.	.
K_{el} (1/hr)	.	.	.	.	.	.	.	.
$ln(C_{max})$	2.197	0.2754	2.225	0.3140	2.249	0.2713	2.198	0.2918
$ln(AUC_{0-t})$	3.981	0.9132	4.104	0.9143	4.153	0.7783	3.918	1.050
$ln(AUC_{0-inf})$	.	.	.	.	.	.	.	.

K_{el} = terminal-phase disposition rate constant; ln = natural logarithm.
Treatment A = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation A.
Treatment B = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation B.
Treatment C = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation C.
Treatment D = a single dose of Premarin 0.45 mg/MPA 1.5 mg (Prempro).

Table 21: Summary of Statistical Comparisons for Unconjugated Δ8,9-Dehydroestrone Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment B vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment C vs Treatment D % Mean Ratio[a]	90% CI[b]
C_{max}	98.67	93.36 - 104.28	102.99	97.55 - 108.74	104.95	99.30 - 110.91
AUC_{0-t}	102.08	86.36 - 120.67	125.11	106.18 - 147.41	125.70	106.36 - 148.56

8. **Unconjugated 17β-Δ8,9-Dehydroestradiol**

Figure 8: Mean (SD) Unconjugated 17β-Δ8,9-Dehydroestradiol concentrations versus time

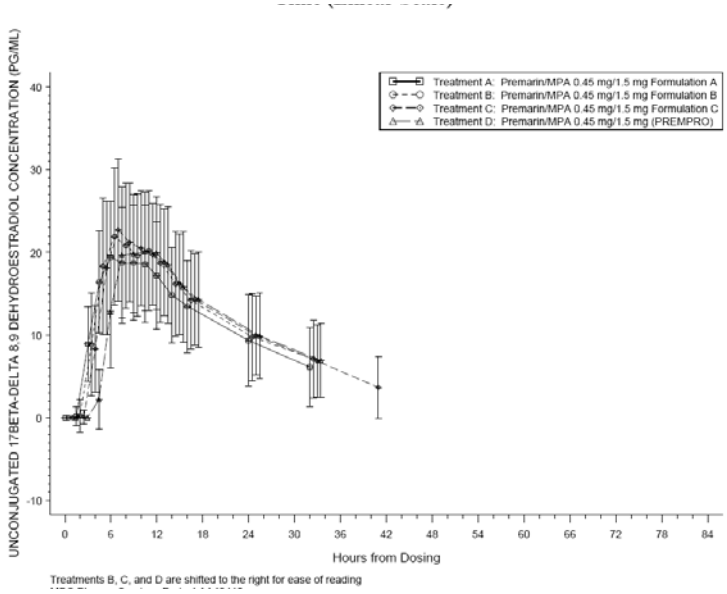


Table 22: Summary of Unconjugated 17β-Δ8,9-Dehydroestradiol Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A Arithmetic Mean	SD	Treatment B Arithmetic Mean	SD	Treatment C Arithmetic Mean	SD	Treatment D Arithmetic Mean	SD
C_{max} (pg/mL)	22.4	6.67	24.8	7.56	25.2	8.14	23.4	7.71
t_{max} (hr)	8.25	4.66	7.97	2.99	7.97	3.40	8.51	2.43
AUC_{0-t} (pg•hr/mL)	411.707	201.606	446.722	211.556	453.270	190.447	427.437	200.344
AUC_{0-inf} (pg•hr/mL)	568.333	227.648	595.964	234.055	608.628	220.267	592.794	227.691
$t_{½}$ (hr)	15.6	6.56	14.8	5.34	16.6	7.00	16.9	8.08
K_{el} (1/hr)	0.0539	0.0266	0.0543	0.0250	0.0498	0.0235	0.0543	0.0408
$ln(C_{max})$	3.062	0.3150	3.163	0.3189	3.172	0.3364	3.099	0.3375
$ln(AUC_{0-t})$	5.876	0.5886	5.972	0.5572	6.010	0.5084	5.930	0.5513
$ln(AUC_{0-inf})$	6.243	0.4892	6.297	0.4738	6.331	0.4398	6.286	0.4987

K_{el} = terminal-phase disposition rate constant; ln = natural logarithm.
Treatment A = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation A.
Treatment B = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation B.
Treatment C = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation C.
Treatment D = a single dose of Premarin 0.45 mg/MPA 1.5 mg (Prempro).

Table 23: Summary of Statistical Comparisons for Unconjugated 17β-Δ8,9-Dehydroestradiol Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment B vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment C vs Treatment D % Mean Ratio[a]	90% CI[b]
C_{max}	95.82	90.48 - 101.48	106.00	100.09 - 112.26	107.58	101.58 - 113.94
AUC_{0-t}	94.52	88.33 - 101.15	103.10	96.35 - 110.33	108.55	101.45 - 116.16
AUC_{0-inf}	94.60	88.59 - 101.02	98.19	91.96 - 104.85	104.69	98.04 - 111.78

Treatment A = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation A.
Treatment B = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation B.
Treatment C = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation C.
Treatment D = a single dose of Premarin 0.45 mg/MPA 1.5 mg (Prempro).

9. **Total Estrone**

Figure 9: Mean (SD) Plasma Total Estrone Concentrations Versus Time

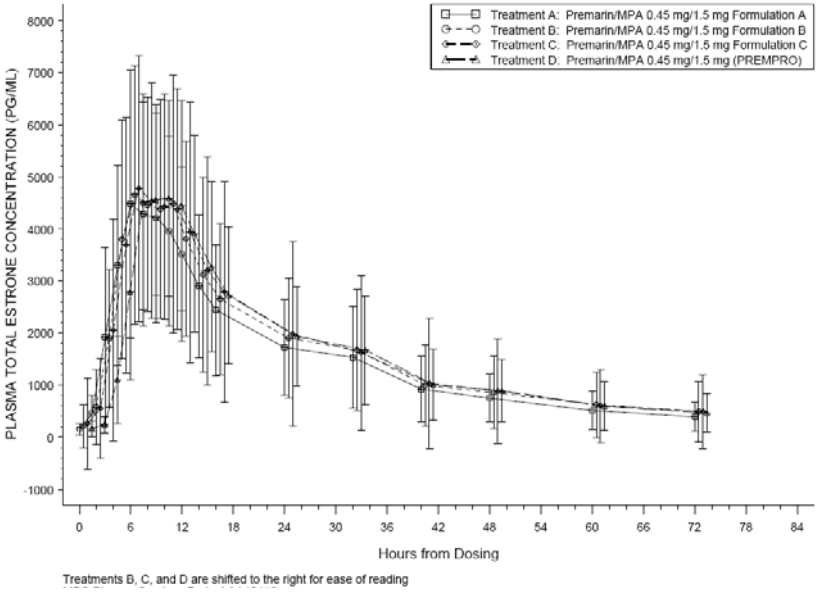


Table 24: Summary of Total Estrone Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A Arithmetic Mean	SD	Treatment B Arithmetic Mean	SD	Treatment C Arithmetic Mean	SD	Treatment D Arithmetic Mean	SD
C_{max} (pg/mL)	5390	2620	5510	2620	5820	3020	5550	2110
t_{max} (hr)	7.94	3.80	8.11	3.20	8.09	3.28	8.92	4.37
AUC_{0-t} (pg•hr/mL)	106347	49651.1	116989	67080.4	118632	87835.2	114948	53647.2
AUC_{0-inf} (pg•hr/mL)	119375	57434.9	132903	94706.0	138227	119188	131653	69490.7
$t_{½}$ (hr)	22.4	11.9	22.2	7.02	22.2	7.14	22.3	7.89
K_{el} (1/hr)	0.0350	0.00992	0.0343	0.0102	0.0342	0.0100	0.0348	0.0117
$ln(C_{max})$	8.487	0.4622	8.519	0.4353	8.564	0.4524	8.547	0.4019
$ln(AUC_{0-t})$	11.48	0.4335	11.56	0.4529	11.56	0.4564	11.56	0.4357
$ln(AUC_{0-inf})$	11.59	0.4373	11.66	0.4830	11.70	0.4534	11.68	0.4630

K_{el} = terminal-phase disposition rate constant; ln = natural logarithm.
Treatment A = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation A.
Treatment B = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation B.
Treatment C = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation C.
Treatment D = a single dose of Premarin 0.45 mg/MPA 1.5 mg (Prempro).

Table 25: Summary of Statistical Comparisons for Total Estrone Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment B vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment C vs Treatment D % Mean Ratio[a]	90% CI[b]
C_{max}	92.79	86.93 - 99.03	96.37	90.29 - 102.85	101.78	95.36 - 108.63
AUC_{0-t}	91.59	87.20 - 96.21	98.74	94.00 - 103.72	100.24	95.43 - 105.30
AUC_{0-inf}	90.82	86.49 - 95.37	96.84	92.15 - 101.77	100.31	95.51 - 105.35

10. **Baseline-Adjusted Total Estrone*****

Figure 10: Mean (SD) Baseline-Adjusted Plasma Total Estrone Concentrations Versus Time

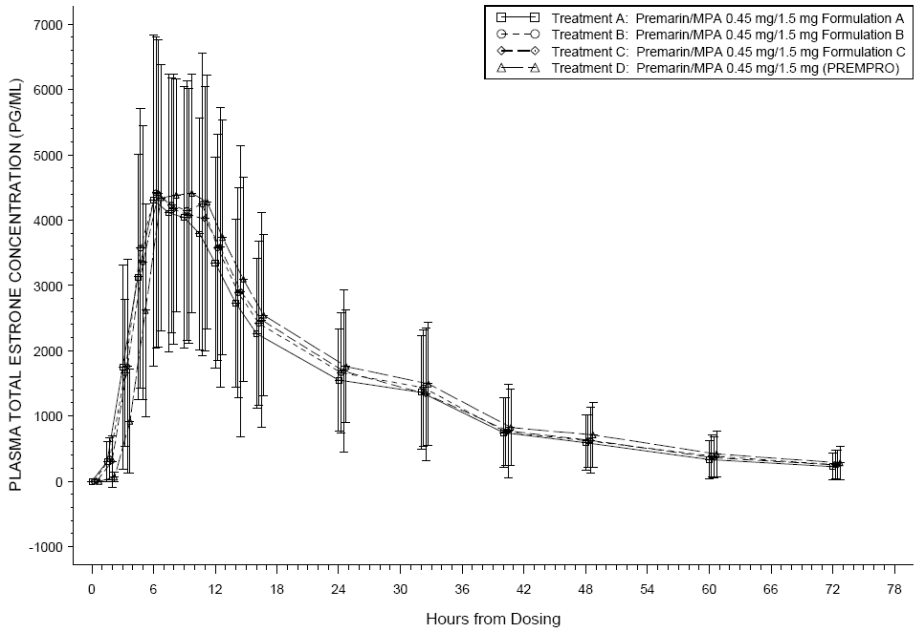


Table 26: Summary of Baseline-Adjusted Total Estrone Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A Arithmetic Mean	SD	Treatment B Arithmetic Mean	SD	Treatment C Arithmetic Mean	SD	Treatment D Arithmetic Mean	SD
C_{max} (pg/mL)	5220	2530	5270	2480	5580	2720	5380	2040
t_{max} (hr)	7.94	3.80	8.11	3.20	8.09	3.28	8.92	4.37
AUC_{0-t} (pg•hr/mL)	94106.4	43101.0	99937.6	47654.7	101421	50535.5	102100	45833.2
AUC_{0-inf} (pg•hr/mL)	99817.2	46951.7	107608	53884.4	108620	55369.9	110237	53183.7
$t_{½}$ (hr)	15.1	4.38	15.9	5.27	16.1	5.58	16.3	5.75
K_{el} (1/hr)	0.0514	0.0241	0.0482	0.0158	0.0481	0.0160	0.0483	0.0200
$ln(C_{max})$	8.451	0.4726	8.474	0.4426	8.526	0.4496	8.513	0.4079
$ln(AUC_{0-t})$	11.36	0.4472	11.42	0.4372	11.43	0.4296	11.44	0.4427
$ln(AUC_{0-inf})$	11.41	0.4539	11.48	0.4503	11.49	0.4481	11.51	0.4630

K_{el} = terminal-phase disposition rate constant; ln = natural logarithm.
Treatment A = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation A.
Treatment B = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation B.
Treatment C = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation C.
Treatment D = a single dose of Premarin 0.45 mg/MPA 1.5 mg (Prempro).

Table 27: Summary of Statistical Comparisons for Baseline-Adjusted Total Estrone Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment B vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment C vs Treatment D % Mean Ratio[a]	90% CI[b]
C_{max}	92.59	86.62 - 98.97	95.27	89.13 - 101.83	101.35	94.82 - 108.33
AUC_{0-t}	91.12	86.27 - 96.23	96.40	91.28 - 101.81	99.45	94.17 - 105.03
AUC_{0-inf}	90.06	85.28 - 95.11	96.41	91.27 - 101.85	98.05	92.82 - 103.57

11. **Total Equilin*****

Figure 11: Mean (SD) Plasma Total Equilin Concentrations Versus Time***

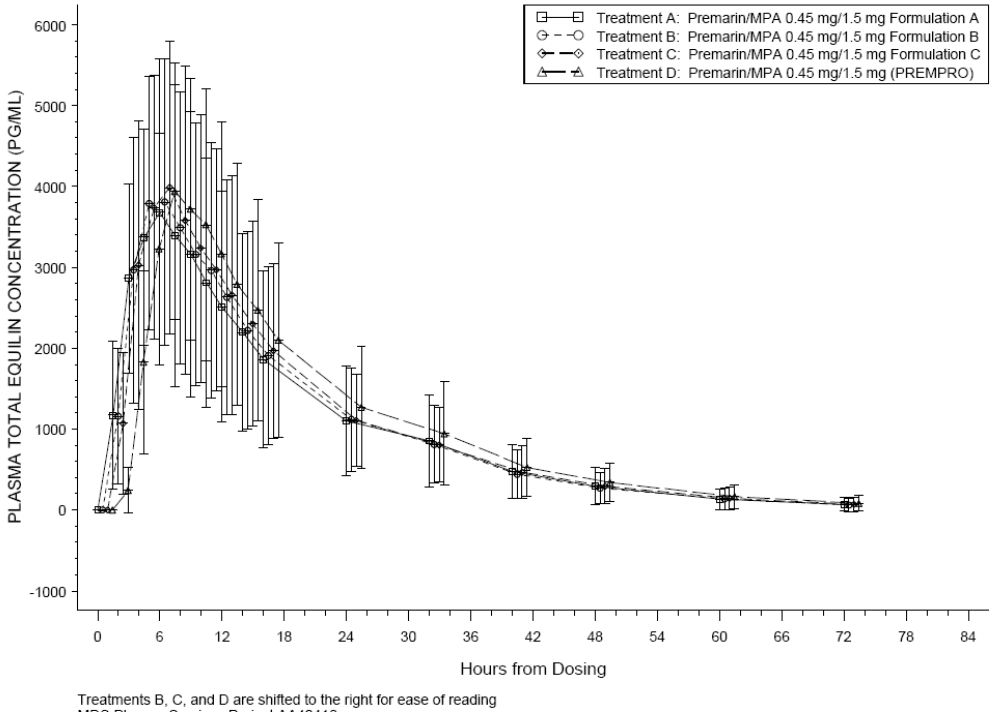


Table 28: Summary of Total Equilin Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A Arithmetic Mean	SD	Treatment B Arithmetic Mean	SD	Treatment C Arithmetic Mean	SD	Treatment D Arithmetic Mean	SD
C_{max} (pg/mL)	4330	1800	4530	1760	4790	2030	4580	1610
t_{max} (hr)	6.49	2.92	5.66	2.20	6.02	2.90	7.86	4.69
AUC_{0-t} (pg•hr/mL)	71980.5	34752.7	73128.2	34215.7	74279.4	31442.7	76276.3	34819.6
AUC_{0-inf} (pg•hr/mL)	73826.3	35622.9	74983.8	35309.5	76280.0	32377.2	78405.6	35943.7
$t_{½}$ (hr)	11.6	3.64	11.6	3.15	11.5	3.60	11.7	3.11
K_{el} (1/hr)	0.0648	0.0176	0.0645	0.0197	0.0676	0.0330	0.0631	0.0170
$ln(C_{max})$	8.288	0.4181	8.345	0.3986	8.393	0.4030	8.361	0.3882
$ln(AUC_{0-t})$	11.08	0.4676	11.11	0.4315	11.13	0.4340	11.14	0.4555
$ln(AUC_{0-inf})$	11.11	0.4623	11.13	0.4294	11.16	0.4324	11.17	0.4514

K_{el} = terminal-phase disposition rate constant; ln = natural logarithm.
Treatment A = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation A.
Treatment B = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation B.
Treatment C = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation C.
Treatment D = a single dose of Premarin 0.45 mg/MPA 1.5 mg (Prempro).

Table 29: Summary of Statistical Comparisons for Total Equilin Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment B vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment C vs Treatment D % Mean Ratio[a]	90% CI[b]
C_{max}	91.72	86.18 - 97.61	97.22	91.35 - 103.47	103.34	97.10 - 109.99
AUC_{0-t}	92.54	87.78 - 97.55	94.80	89.94 - 99.94	98.52	93.47 - 103.85
AUC_{0-inf}	92.39	87.68 - 97.35	94.52	89.71 - 99.59	98.37	93.36 - 103.64

12. **Total 17β-Estradiol**

Figure 12: Mean (SD) plasma total 17β-Estradiol concentration versus time

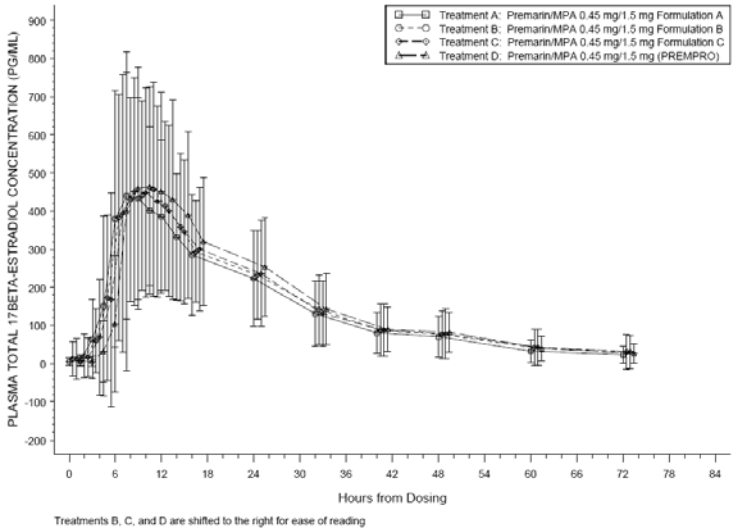


Table 30: Summary of Total 17β-Estradiol Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A Arithmetic Mean	SD	Treatment B Arithmetic Mean	SD	Treatment C Arithmetic Mean	SD	Treatment D Arithmetic Mean	SD
C_{max} (pg/mL)	613	307	609	312	636	341	675	384
t_{max} (hr)	10.9	5.75	11.1	5.94	11.6	6.05	11.1	5.59
AUC_{0-t} (pg•hr/mL)	10151.9	4717.49	10846.1	5233.42	10810.3	5463.32	11194.4	5087.52
AUC_{0-inf} (pg•hr/mL)	10891.6	5082.05	12448.8	9492.38	11931.7	7968.73	12005.6	5651.17
$t_{½}$ (hr)	16.8	7.94	18.3	14.4	18.6	14.5	15.6	6.18
K_{el} (1/hr)	0.0481	0.0174	0.0462	0.0159	0.0469	0.0177	0.0513	0.0208
$ln(C_{max})$	6.287	0.5322	6.287	0.5048	6.319	0.5304	6.350	0.5949
$ln(AUC_{0-t})$	9.129	0.4415	9.197	0.4283	9.193	0.4271	9.227	0.4517
$ln(AUC_{0-inf})$	9.202	0.4312	9.287	0.4783	9.268	0.4517	9.298	0.4381

K_{el} = terminal-phase disposition rate constant; ln = natural logarithm.
Treatment A = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation A.
Treatment B = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation B.
Treatment C = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation C.
Treatment D = a single dose of Premarin 0.45 mg/MPA 1.5 mg (Prempro).

Table 31: Summary of Statistical Comparisons for Total 17β-Estradiol Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment B vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment C vs Treatment D % Mean Ratio[a]	90% CI[b]
C_{max}	92.80	85.78 - 100.38	93.10	86.06 - 100.71	96.87	89.55 - 104.79
AUC_{0-t}	90.01	83.85 - 96.62	96.00	89.43 - 103.04	96.47	89.87 - 103.56
AUC_{0-inf}	90.23	83.83 - 97.13	97.14	90.18 - 104.63	96.78	89.87 - 104.21

13. **Baseline-Adjusted Total 17β-Estradiol**

Figure 13: Mean (SD) baseline-adjusted total 17β-Estradiol concentration verus time

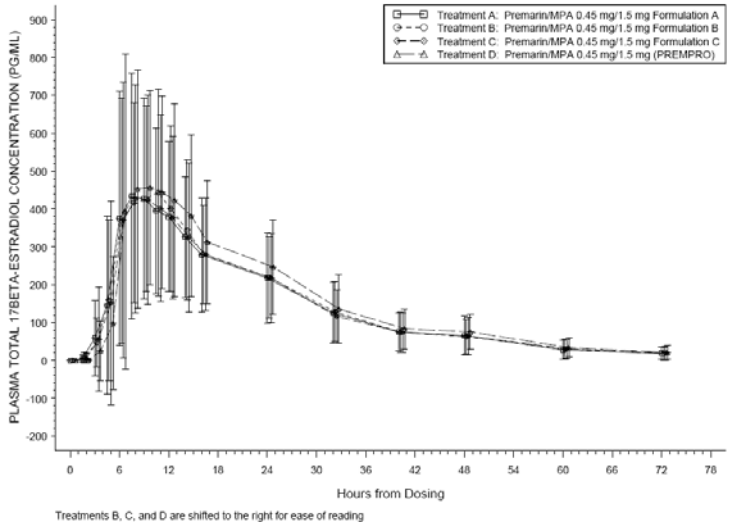


Table 32: Summary of Baseline-Adjusted Total 17β-Estradiol Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A Arithmetic Mean	SD	Treatment B Arithmetic Mean	SD	Treatment C Arithmetic Mean	SD	Treatment D Arithmetic Mean	SD
C_{max} (pg/mL)	607	304	595	306	624	333	668	380
t_{max} (hr)	10.9	5.75	11.1	5.94	11.6	6.05	11.1	5.59
AUC_{0-t} (pg•hr/mL)	9710.42	4410.66	9858.08	4229.52	9925.89	3910.07	10665.1	4630.39
AUC_{0-inf} (pg•hr/mL)	10240.3	4626.84	10524.7	4336.71	10513.2	4086.54	11436.2	4693.09
$t_{½}$ (hr)	14.8	5.99	14.7	7.06	15.6	8.02	13.6	4.76
K_{el} (1/hr)	0.0533	0.0190	0.0551	0.0260	0.0539	0.0225	0.0570	0.0198
$ln(C_{max})$	6.275	0.5390	6.254	0.5382	6.300	0.5280	6.336	0.6050
$ln(AUC_{0-t})$	9.082	0.4577	9.100	0.4635	9.131	0.3850	9.177	0.4676
$ln(AUC_{0-inf})$	9.138	0.4485	9.180	0.4167	9.190	0.3790	9.264	0.4131

K_{el} = terminal-phase disposition rate constant; ln = natural logarithm.
Treatment A = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation A.
Treatment B = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation B.
Treatment C = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation C.
Treatment D = a single dose of Premarin 0.45 mg/MPA 1.5 mg (Prempro).

Table 33: Summary of Statistical Comparisons for Baseline-Adjusted Total 17β-Estradiol Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment B vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment C vs Treatment D % Mean Ratio[a]	90% CI[b]
C_{max}	92.97	85.83 - 100.71	91.26	84.25 - 98.86	96.47	89.06 - 104.50
AUC_{0-t}	90.38	83.77 - 97.51	91.65	84.95 - 98.88	95.34	88.37 - 102.87
AUC_{0-inf}	88.02	82.16 - 94.30	90.60	84.48 - 97.17	93.14	86.94 - 99.79

14. **Total 17β-Dihydroequilin**

Figure 14: Mean (SD) plasma Total 17β-Dihydroequilin concentration versus time

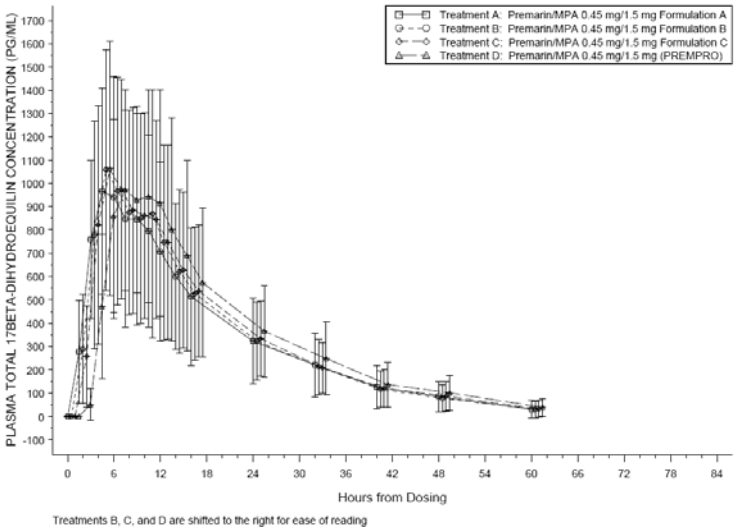


Table 34: Summary of Total 17β-Dihydroequilin Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A Arithmetic Mean	SD	Treatment B Arithmetic Mean	SD	Treatment C Arithmetic Mean	SD	Treatment D Arithmetic Mean	SD
C_{max} (pg/mL)	1190	504	1220	555	1310	545	1220	491
t_{max} (hr)	6.32	3.15	5.91	2.60	6.07	2.96	8.15	4.71
AUC_{0-t} (pg•hr/mL)	19408.8	9017.62	19716.6	9391.85	20053.8	8216.60	20551.2	9388.20
AUC_{0-inf} (pg•hr/mL)	20374.9	9110.62	20446.3	9612.55	20917.5	8455.96	21346.1	9692.53
$t_{½}$ (hr)	11.9	4.19	11.4	3.25	11.7	3.45	11.8	3.46
K_{el} (1/hr)	0.0642	0.0211	0.0660	0.0219	0.0659	0.0321	0.0637	0.0186
$ln(C_{max})$	6.999	0.4203	7.011	0.4336	7.093	0.4112	7.028	0.4146
$ln(AUC_{0-t})$	9.777	0.4469	9.795	0.4305	9.825	0.4170	9.834	0.4513
$ln(AUC_{0-inf})$	9.835	0.4218	9.837	0.4166	9.869	0.4138	9.875	0.4441

K_{el} = terminal-phase disposition rate constant; ln = natural logarithm.
Treatment A = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation A.
Treatment B = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation B.
Treatment C = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation C.
Treatment D = a single dose of Premarin 0.45 mg/MPA 1.5 mg (Prempro).

Table 35: Summary of Statistical Comparisons for Total 17β-Dihydroequilin Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment B vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment C vs Treatment D % Mean Ratio[a]	90% CI[b]
C_{max}	95.63	89.75 - 101.88	97.05	91.09 - 103.40	106.81	100.25 - 113.80
AUC_{0-t}	93.37	88.45 - 98.56	95.03	90.02 - 100.31	99.15	93.93 - 104.66
AUC_{0-inf}	95.01	90.15 - 100.13	95.19	90.35 - 100.29	99.35	94.28 - 104.70

15. **Total Δ8,9-Dehydroestrone**

Figure 15: Mean (SD) plasma Total Δ8,9-Dehydroestrone concentration versus time

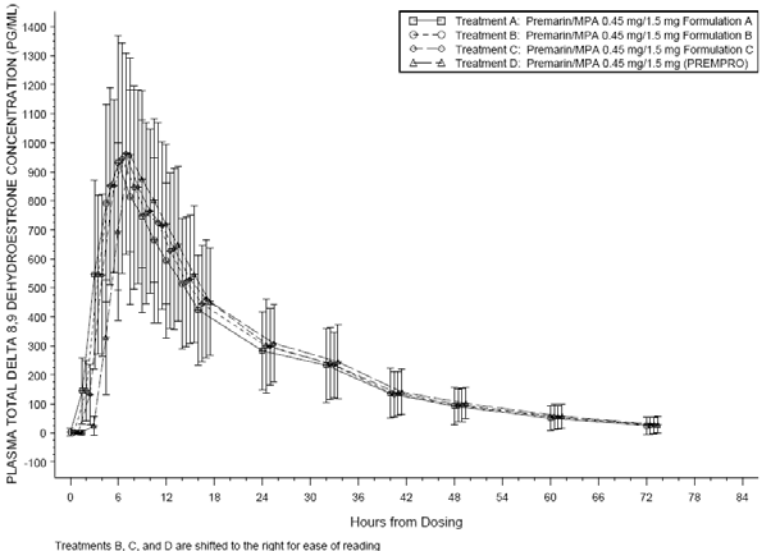


Table 36: Summary of Total Δ8,9-Dehydroestrone Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A Arithmetic Mean	SD	Treatment B Arithmetic Mean	SD	Treatment C Arithmetic Mean	SD	Treatment D Arithmetic Mean	SD
C_{max} (pg/mL)	1040	460	1040	399	1070	341	1030	328
t_{max} (hr)	6.52	2.10	6.09	1.77	6.34	2.08	7.49	3.59
AUC_{0-t} (pg•hr/mL)	17756.1	7532.27	18413.0	7846.22	18520.7	6540.46	18266.7	6708.40
AUC_{0-inf} (pg•hr/mL)	18725.0	7855.06	19382.3	8331.59	19524.7	6868.83	19283.0	7002.63
$t_{½}$ (hr)	14.3	3.40	14.3	3.65	14.5	4.00	14.6	3.60
K_{el} (1/hr)	0.0515	0.0135	0.0514	0.0131	0.0545	0.0347	0.0510	0.0156
$ln(C_{max})$	6.867	0.3975	6.882	0.3603	6.921	0.3234	6.880	0.3630
$ln(AUC_{0-t})$	9.699	0.4254	9.741	0.4008	9.762	0.3736	9.743	0.3867
$ln(AUC_{0-inf})$	9.755	0.4148	9.793	0.3963	9.816	0.3702	9.801	0.3722

K_{el} = terminal-phase disposition rate constant; ln = natural logarithm.
Treatment A = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation A.
Treatment B = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation B.
Treatment C = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation C.
Treatment D = a single dose of Premarin 0.45 mg/MPA 1.5 mg (Prempro).

Table 37: Summary of Statistical Comparisons for Total Δ8,9-Dehydroestrone Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment B vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment C vs Treatment D % Mean Ratio[a]	90% CI[b]
C_{max}	97.74	91.76 - 104.11	99.48	93.39 - 105.96	104.42	98.03 - 111.23
AUC_{0-t}	94.67	90.07 - 99.50	98.35	93.58 - 103.37	102.05	97.10 - 107.26
AUC_{0-inf}	94.53	90.08 - 99.21	97.76	93.15 - 102.59	101.60	96.82 - 106.62

16. **Total 17β-Δ8,9-Dehydroestradiol**

Figure 16: Mean (SD) plasma Total 17β-Δ8,9-Dehydroestradiol concentration versus time

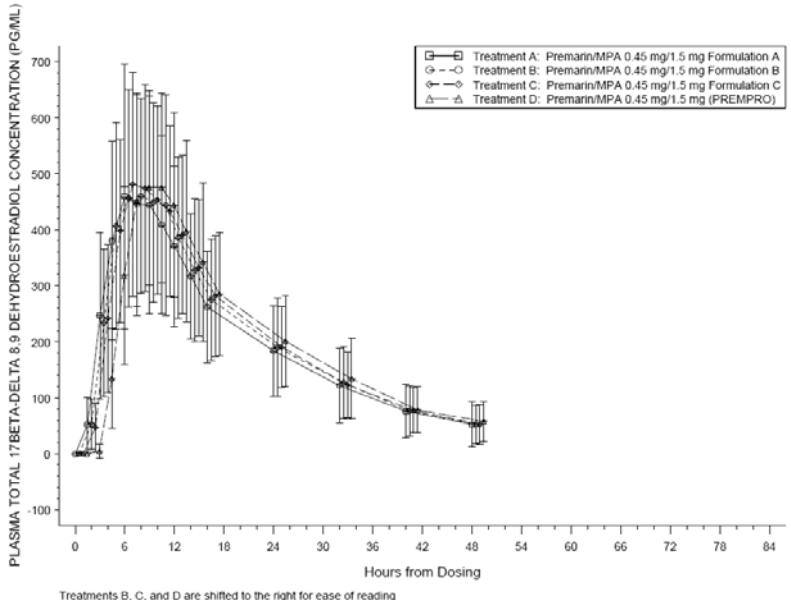


Table 38: Summary of Total 17β-Δ8,9-Dehydroestradiol Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A Arithmetic Mean	SD	Treatment B Arithmetic Mean	SD	Treatment C Arithmetic Mean	SD	Treatment D Arithmetic Mean	SD
C_{max} (pg/mL)	568	226	546	207	574	186	577	187
t_{max} (hr)	7.49	2.52	7.39	2.49	7.63	2.77	8.75	4.06
AUC_{0-t} (pg•hr/mL)	9867.39	3878.07	10158.0	4042.71	10274.9	3323.31	10220.8	3593.34
AUC_{0-inf} (pg•hr/mL)	10656.2	4009.39	10882.7	4258.95	11027.5	3474.57	11027.1	3736.47
$t_{½}$ (hr)	14.1	4.34	13.6	3.81	13.3	3.91	13.9	3.81
K_{el} (1/hr)	0.0535	0.0158	0.0551	0.0177	0.0586	0.0287	0.0549	0.0224
$ln(C_{max})$	6.263	0.4084	6.233	0.3781	6.299	0.3403	6.301	0.3476
$ln(AUC_{0-t})$	9.119	0.4114	9.152	0.3910	9.180	0.3588	9.167	0.3814
$ln(AUC_{0-inf})$	9.204	0.3875	9.227	0.3721	9.253	0.3530	9.248	0.3672

K_{el} = terminal-phase disposition rate constant; ln = natural logarithm.
Treatment A = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation A.
Treatment B = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation B.
Treatment C = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation C.
Treatment D = a single dose of Premarin 0.45 mg/MPA 1.5 mg (Prempro).

Table 39: Summary of Statistical Comparisons for Total 17β-Δ8,9-Dehydroestradiol Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment B vs Treatment D % Mean Ratio[a]	90% CI[b]	Treatment C vs Treatment D % Mean Ratio[a]	90% CI[b]
C_{max}	95.27	90.08 - 100.77	92.76	87.70 - 98.11	99.75	94.31 - 105.51
AUC_{0-t}	94.60	89.40 - 100.10	97.52	92.17 - 103.20	101.36	95.79 - 107.25
AUC_{0-inf}	95.31	90.30 - 100.60	97.20	92.09 - 102.60	100.90	95.60 - 106.50

17. **Medroxyprogesterone Acetate*****

Figure 17: Mean (SD) Plasma Medroxyprogesterone Acetate Concentrations Versus Time

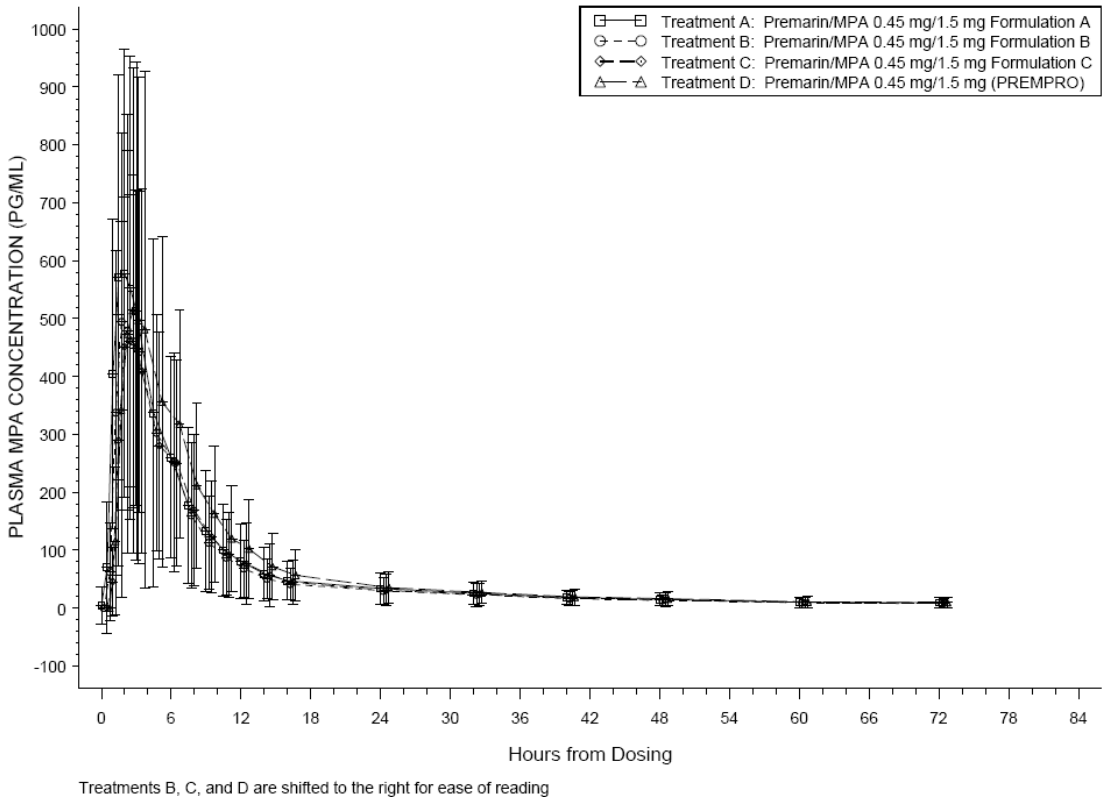


Table 40: Summary of Medroxyprogesterone Acetate Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A Arithmetic Mean	SD	Treatment B Arithmetic Mean	SD	Treatment C Arithmetic Mean	SD	Treatment D Arithmetic Mean	SD
C_{max} (pg/mL)	724	475	617	340	573	338	673	487
t_{max} (hr)	1.95	1.01	2.00	0.838	2.12	1.42	2.69	1.74
AUC_{0-t} (pg•hr/mL)	4517.76	2745.67	3963.58	2252.56	3937.20	2374.85	4768.16	2955.94
AUC_{0-inf} (pg•hr/mL)	4962.74	3037.84	4453.72	2524.06	4455.76	2617.40	5393.94	3259.66
$t_{½}$ (hr)	26.2	9.68	26.1	9.90	25.7	8.80	27.6	9.05
K_{el} (1/hr)	0.0310	0.0185	0.0331	0.0277	0.0326	0.0234	0.0276	0.00854
$ln(C_{max})$	6.400	0.6127	6.278	0.5584	6.209	0.5360	6.294	0.6574
$ln(AUC_{0-t})$	8.230	0.6335	8.121	0.5917	8.103	0.6102	8.286	0.6216
$ln(AUC_{0-inf})$	8.322	0.6353	8.241	0.5819	8.236	0.5929	8.415	0.6138

K_{el} = terminal-phase disposition rate constant; ln = natural logarithm.
Treatment A = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation A.
Treatment B = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation B.
Treatment C = a single dose of Premarin 0.45 mg/MPA 1.5 mg formulation C.
Treatment D = a single dose of Premarin 0.45 mg/MPA 1.5 mg (Prempro).

Table 41: Summary of Statistical Comparisons for Medroxyprogesterone Acetate Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A vs Treatment D		Treatment B vs Treatment D		Treatment C vs Treatment D	
	% Mean Ratio[a]	90% CI[b]	% Mean Ratio[a]	90% CI[b]	% Mean Ratio[a]	90% CI[b]
C_{max}	110.26	98.42 - 123.53	97.66	87.17 - 109.41	91.73	81.87 - 102.78
AUC_{0-t}	93.85	85.95 - 102.48	84.41	77.30 - 92.17	83.35	76.34 - 91.02
AUC_{0-inf}	91.21	83.54 - 99.59	83.07	76.01 - 90.78	82.76	75.71 - 90.46

21 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

Doanh Tran
10/23/2008 11:26:32 AM
BIOPHARMACEUTICS

Chongwoo Yu
10/23/2008 01:11:54 PM
BIOPHARMACEUTICS

Hae-Young Ahn
10/23/2008 04:09:25 PM
BIOPHARMACEUTICS

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	**20527/SCF 046**
Submission Date:	6/25/2008
Brand Name:	Prempro
Generic Name:	Conjugated Estrogen/medroxyprogesterone acetate
Formulation:	Tablets
Strength:	0.3 mg/1.5 mg, 0.45 mg/1.5 mg, 0.625 mg/2.5 mg, and 0.625 mg/5 mg
Sponsor:	Wyeth
Reviewer:	John Duan, Ph.D.
Submission Type:	Dissolution Comparisons

BACKGROUND

The major issue for biopharmaceutics is the biowaiver request for reformulated 0.3 mg/1.5 mg strength, which is the lower strength of the two reformulated strengths. OCP review has accepted the higher strength (0.45 mg/1.5 mg) BE comparison study. This review will examine the lower strength dissolution comparison to determine if the biowaiver can be granted.

DISSOLTION COMPARISON

The following tables summarize the dissolution comparison results. For conjugated estrogen (CE), two dissolution methods were used, and for medroxyprogesterone acetate (MPA), three dissolution methods were used as shown in the following notations appeared as superscript at each batch number in the tables.

a. CE dissolution method conditions: 0.02M sodium acetate buffer, pH 4.5, 900 mL, Apparatus 2, 50 rpm (Method L26095-200).
b. MPA dissolution method conditions: 0.54% SLS, 900 mL, Apparatus 2, 50 rpm (Method L26403-009).
c. MPA dissolution method conditions: 0.54% SLS, 900 mL, Apparatus 2, 100 rpm (Method L33354-040)
d. MPA dissolution method conditions: 0.54% SLS, 900 mL, Apparatus – modified disintegration (Method L18623-045)
e. CE dissolution method conditions: water, 900 mL, Apparatus 2, 50 rpm (Method L 18713-057)

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

As shown, all the 0.30 mg/1.5 mg batches used method “a” for CE and method “b” for MPA. Under the same dissolution method, using five 0.45 mg/1.5 mg batches as references (2007B0009, 2006B0013, 2005B0324, 2007B0010, and 2007B0011) for CE and three 0.45 mg/1.5 mg batches as references (2007B0009, 2007B0010, and 2007B0011) fro MPA, the calculated f2 factors are all more than 50, demonstrating the similarity.

When using the two batches (2006B0013 and 2005B0324), which using method “c” (increasing the paddle speed from 50 to 100 rpm), as reference for MPA, the f2 factors are (b) (4) This is understandable due to the different paddle speeds, indicating the dissolution is condition dependent.

COMMENTS

Based on the above calculations, the similarity between two strengths has been shown. Although the biowaiver may be granted according to the dissolution method used, the following issues have not been and should be resolved before an approval.

1. The current proposed dissolution method for MPA (L26403-009) is different from previous methods (L18623-045, these method numbers were provided by review Chemist, Dr. Jean Salemme). The difference is not clearly stated in the submission. The sponsor should provide a side by side comparison between the new dissolution method and the previous approved method.
2. Due to the new dissolution method developed and the strengths newly reformulated, dissolution method and specification should be appropriately justified including use of apparatus, dissolution medium, dissolution pH, and agitation speed.
3. After the dissolution method is properly justified, dissolution specification should be proposed according to adequate amount of dissolution data.
4. After the dissolution method is properly justified, the dissolution profile comparison should be performed between the reformulated 0.3 mg/1.5 mg strength and the reformulated 0.45 mg/1.5 mg batch, which were used in the bioequivalence study.
5. The dissolution comparison study should be provided in detail. Specifically, the following data should be included.

    - All the raw dissolution data (with at least 12 individual dosage units and the percent coefficient of variation at the each time point).
    - f2 calculations according to the FDA Guidance, with use of not more than one data point past (b) (4) % dissolved.

RECOMMENDATION

Please convey the comments to the review chemist.

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

cc: NDA 20527
Patrick Marroum, John Duan

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

/s/

John Duan
10/23/2008 04:22:44 PM
BIOPHARMACEUTICS
Since Dr. Patrick Marroum did not have DFS access,
he authorized me to do the final sign
off. He has reviewed the document.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 020527/S-046

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: March 30, 2009

To: Robert DiGregorio	**From:** George Lyght
Company: Wyeth Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 484-865-4323	**Fax number:** 301-796-9897
Phone number: 484-865-8424	**Phone number:** 301-796-0948

Subject: NDA 20-527/046 Prempro tablets
Carton, blister pack and bottle label

Total no. of pages including cover: 2

Comments:

Document to be mailed: ❑ **YES** ☑ **NO**

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 this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1218. Thank you.

The following has been identified to be addressed in NDA 20-527/S-046:

(b) (4)

Amend the carton, bottle label and blister pack to show an established name that is (b) (4) **of the Tradename.**

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

/s/

George Lyght
4/7/2009 10:52:39 AM
CSO

George Lyght
4/7/2009 10:53:11 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-527/S-046 **PRIOR APPROVAL SUPPLEMENT**

Wyeth Pharmaceuticals Inc.
Attention: Christian D. Le
Sr. Regulatory Specialist, Global Regulatory Affairs, CMC
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Le:

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

Name of Drug Product:	Prempro™ Premphase® (conjugated estrogens/medroxyprogesterone acetate) Tablet
NDA Number:	20-527
Supplement number:	S-046
Date of supplement:	June 25, 2008
Date of receipt:	June 25, 2008

This supplemental application proposes the following change(s): reformation of Prempro 0.3 mg/1.5 mg and 0.45 mg/1.5 mg tablets.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 24, 2008 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 25, 2008.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproduction and Urology
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call me at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Cathy Tran-Zwanetz
Regulatory Health Project Manager
Division of Post-Marketing Evaluation
Office of New Drug Quality Assessment
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/

Catherine Tran-Zwanetz

8/13/2008 04:33:48 PM