CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 04-782/S-115 & S-130

Name: Premarin Tablets

Generic Name: conjugated estrogen, USP

Sponsor: Wyeth Pharmaceuticals

Approval Date: 04/24/2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 04-782/S-115 & S-130

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 04-782/S-115 & S-130

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 04-782/S-115 and S-130

APPROVAL LETTER

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

Dear Ms. Norman:

Please refer to your supplemental new drug applications dated July 31, 2000, received July 31, 2000, (S-115) and February 11, 2003, received February 13, 2003, (S-130) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Premarin® (conjugated estrogens, USP) tablets.

We acknowledge receipt of your submissions dated October 15 and 28, 2002 and April 7 and 10, 2003 to S-115. Your October 15, 2002 submission constituted a complete response to our approvable letter of July 31, 2001.

We also acknowledge receipt of your submission dated February 20, 2003 (S-130).

These supplemental new drug applications provide for:

1. The use of Premarin® (0.45 mg) for the treatment of moderate to-severe vasomotor symptoms associated with the menopause and for the treatment of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. (S-115).

2. Revisions in the text of the **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION AND HOW SUPPLIED** sections of the package insert, and the text of the patient package insert (S-115 and 130).

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

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

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 04-782/S-115, S-130." Approval of this submission by FDA is not required before the labeling is used.

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

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure

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

/s/

Daniel A. Shames
4/24/03 04:02:05 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 04-782/S-115 & S-130

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 4-782/S-115

Wyeth Ayerst Laboratories
Attention: Joseph S. Sonk, Ph.D.
Senior Director, Therapeutic Head, Women's Health,
Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101

Dear Dr. Sonk:

Please refer to your supplemental new drug application dated July 31, 2000, received July 31, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Premarin® (conjugated estrogens, USP) tablets, 0.45 mg.

We acknowledge receipt of your submissions dated October 24, November 22 and 30, 2000; January 11, February 2, March 13 and 14, April 2, May 9, 15 and 24, and June 5, 12 and 29, 2001.

This supplemental new drug application proposes the use of Premarin (0.45 mg) for the treatment of moderate-to-severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. During recent inspections of the Guayama, Puerto Rico manufacturing facility for your supplement, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. A satisfactory inspection of this facility will be required before this application may be approved.

2. During recent inspections of the Rouses Point, New York manufacturing facility for your supplement, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. A satisfactory inspection of this facility will be required before this application may be approved.

3. Please submit final printed labeling (FPL) revised as enclosed. Additions have been noted with single underlining, deletions have been noted as ~~strikeouts~~. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

4. The storage statement on the container and carton labels should be revised to "Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature]"

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry entitled, "Providing Regulatory Submissions in Electronic Format – NDA (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Diane Moore, BS, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

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

Enclosure:

32 page(s) of draft labeling has been removed from this portion of the review.

Approvable Letter

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

/s/

Susan Allen
7/31/01 03:34:58 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 04-782/S-115 & S-130

FINAL PRINTED LABELING

Premarin®

(conjugated estrogens tablets, USP)

℞ only

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens 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.

CARDIOVASCULAR AND OTHER RISKS

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease.

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

DESCRIPTION

PREMARIN® (CONJUGATED ESTROGENS TABLETS, USP) FOR ORAL ADMINISTRATION CONTAINS A MIXTURE OF CONJUGATED EQUINE ESTROGENS OBTAINED EXCLUSIVELY FROM NATURAL SOURCES, OCCURRING AS THE SODIUM SALTS OF WATER-SOLUBLE ESTROGEN SULFATES BLENDED TO REPRESENT THE AVERAGE COMPOSITION OF MATERIAL DERIVED FROM PREGNANT MARES' URINE. IT IS A MIXTURE OF SODIUM ESTRONE SULFATE AND SODIUM EQUILIN SULFATE. IT CONTAINS AS CONCOMITANT COMPONENTS, AS SODIUM SULFATE CONJUGATES, 17α-DIHYDROEQUILIN, 17α-ESTRADIOL, AND 17β-DIHYDROEQUILIN. TABLETS FOR ORAL ADMINISTRATION ARE AVAILABLE IN 0.3 MG, 0.45 MG, 0.625 MG, 0.9 MG, 1.25 MG, AND 2.5 MG STRENGTHS OF CONJUGATED ESTROGENS.

PREMARIN TABLETS CONTAIN THE FOLLOWING INACTIVE INGREDIENTS: CALCIUM PHOSPHATE TRIBASIC, CALCIUM SULFATE, CARNAUBA WAX, CELLULOSE, GLYCERYL MONOOLEATE, LACTOSE, MAGNESIUM STEARATE, METHYLCELLULOSE, PHARMACEUTICAL GLAZE, POLYETHYLENE GLYCOL, STEARIC ACID (NOT PRESENT IN 0.45 MG TABLET), SUCROSE, AND TITANIUM DIOXIDE.

— 0.3 mg tablets also contain: D&C Yellow No. 10, FD&C Blue No. 1, FD&C Blue No. 2, FD&C Yellow No. 6; these tablets comply with USP Drug Release Test 1.

— 0.45 MG TABLETS ALSO CONTAIN: FD&C BLUE NO. 2; THESE TABLETS COMPLY WITH USP DRUG RELEASE TEST 1.

— 0.625 mg tablets also contain: FD&C Blue No. 2, D&C Red No. 27, FD&C Red No. 40; these tablets comply with USP Drug Release Test 1.

— 0.9 mg tablets also contain: D&C Red No. 6, D&C Red No. 7; these tablets comply with USP Drug Release Test 2.

— 1.25 mg tablets also contain: black iron oxide, D&C Yellow No. 10, FD&C Yellow No. 6; these tablets comply with USP Drug Release Test 3.

— 2.5 mg tablets also contain: FD&C Blue No. 2, D&C Red No. 7; these tablets comply with USP Drug Release Test 3.

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.

PHARMACOKINETICS

ABSORPTION

CONJUGATED ESTROGENS ARE SOLUBLE IN WATER AND ARE WELL ABSORBED FROM THE GASTROINTESTINAL TRACT AFTER RELEASE FROM THE DRUG FORMULATION. THE PREMARIN TABLET RELEASES CONJUGATED ESTROGENS SLOWLY OVER SEVERAL HOURS. TABLE 1 SUMMARIZES THE MEAN PHARMACOKINETIC PARAMETERS FOR UNCONJUGATED AND CONJUGATED ESTROGENS FOLLOWING ADMINISTRATION OF 2 X 0.3 MG, 2 X 0.45 MG, AND 2 X 0.625 MG TABLETS TO HEALTHY POSTMENOPAUSAL WOMEN.

TABLE 1. PHARMACOKINETIC PARAMETERS FOR PREMARIN

1.2.5.2.1.1.1.1 Pharmacokinetic Profile of Unconjugated Estrogens Following a Dose of 2 x 0.3 mg

PK Parameter Arithmetic Mean (%CV)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)
Estrone	82 (33)	7.8 (27)	54.7 (42)	5390 (50)
Baseline-adjusted estrone	58 (42)	7.8 (27)	21.1 (45)	1467 (41)
Equilin	31 (47)	7.2 (28)	18.3 (110)	652 (68)

Pharmacokinetic Profile of Conjugated Estrogens Following a Dose of 2 x 0.3 mg

PK Parameter Arithmetic Mean (%CV)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
Estrone	2.5 (32)	6.5 (29)	25.4 (22)	61.0 (43)
Baseline-adjusted total estrone	2.4 (32)	6.5 (29)	16.2 (34)	40.8 (36)
Equilin	1.6 (40)	5.9 (27)	11.8 (21)	22.4 (42)

1.2.5.2.1.1.1.2 Pharmacokinetic Profile of Unconjugated Estrogens Following a Dose of 2 x 0.45 mg

PK Parameter Arithmetic Mean (%CV)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)
.1.2 Estrone	**2.1.3 92 (32)**	**2.1.4 8.7 (28)**	**.2.1.5 56.4 (68)**	**.2.1.6 6344 (56)**
.1.7 Baseline-adjusted estrone	**2.1.8 65 (40)**	**2.1.9 8.7 (28)**	**2.1.10 20.3 (38)**	**2.1.11 1940 (40)**
Equilin	35 (49)	7.6 (33)	21.9 (113)	849 (60)

1.2.5.2.1.11.1.1

1.2.5.2.1.11.1.2 Pharmacokinetic Profile of Conjugated Estrogens Following a Dose of 2 x 0.45 mg

PK Parameter Arithmetic Mean (%CV)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
.1.12 Total estrone	2.8 (46)	7.1 (27)	27.6 (35)	77 (34)
.1.13 Baseline-adjusted total estrone	2.6 (46)	7.1 (27)	14.7 (42)	48 (38)
Total equilin	1.9 (53)	5.9 (32)	11.8 (32)	29 (55)

1.2.5.2.1.13.1.1 Pharmacokinetic Profile of Unconjugated Estrogens Following a Dose of 2 x 0.625 mg

PK Parameter Arithmetic Mean (%CV)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)
.1.14 Estrone	**.1.15 139 (37)**	**:.1.16 8.8 (20)**	**2.1.17 28.0 (30)**	**2.1.18 5016 (34)**
.1.19 Baseline-adjusted estrone	**.1.20 120 (41)**	**:.1.21 8.8 (20)**	17.4 (37)	**2.1.22 2956 (39)**
Equilin	66 (42)	7.9 (19)	13.6 (52)	1210 (37)

1.2.5.2.1.22.1.1

1.2.5.2.1.22.1.2 Pharmacokinetic Profile of Conjugated Estrogens Following a Dose of 2 x 0.625 mg

PK Parameter Arithmetic Mean (%CV)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
Total estrone	7.3 (41)	7.3 (24)	15.0 (25)	134 (42)
Baseline-adjusted total estrone	7.1 (41)	7.3 (24)	13.6 (23)	122 (38)
Total equilin	5.0 (42)	6.2 (26)	10.1 (26)	65 (44)

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 concentration in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism
EXOGENOUS ESTROGENS ARE METABOLIZED IN THE SAME MANNER AS ENDOGENOUS ESTROGENS. CIRCULATING ESTROGENS EXIST IN A DYNAMIC EQUILIBRIUM OF METABOLIC INTERCONVERSIONS. THESE TRANSFORMATIONS TAKE PLACE MAINLY IN THE LIVER. ESTRADIOL IS CONVERTED REVERSIBLY TO ESTRONE, AND BOTH CAN BE CONVERTED TO ESTRIOL, WHICH IS THE MAJOR URINARY METABOLITE. ESTROGENS ALSO UNDERGO ENTEROHEPATIC RECIRCULATION VIA SULFATE AND GLUCURONIDE CONJUGATION IN THE LIVER, BILIARY SECRETION OF CONJUGATES INTO THE INTESTINE, AND HYDROLYSIS IN THE GUT FOLLOWED BY REABSORPTION. IN POSTMENOPAUSAL WOMEN A SIGNIFICANT PROPORTION OF THE CIRCULATING ESTROGENS EXISTS AS SULFATE CONJUGATES, ESPECIALLY ESTRONE SULFATE, WHICH SERVES AS A CIRCULATING RESERVOIR FOR THE FORMATION OF MORE ACTIVE ESTROGENS.

Excretion
ESTRADIOL, ESTRONE, AND ESTRIOL ARE EXCRETED IN THE URINE ALONG WITH GLUCURONIDE AND SULFATE CONJUGATES.

1.2.6 Special Populations
NO PHARMACOKINETIC STUDIES WERE CONDUCTED IN SPECIAL POPULATIONS, INCLUDING PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT.

1.2.7 Drug Interactions
Data from a single-dose drug-drug interaction study involving conjugated estrogens and medroxyprogesterone acetate indicate that the pharmacokinetic dispositions of both drugs are not significantly altered. 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.

1.2.8 Clinical Studies
Effects on Vasomotor Symptoms
In the first year of the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, a total of 2805 postmenopausal women (average age 53.3 ± 4.9 years) were randomly assigned to one of eight treatment groups, receiving either placebo or conjugated estrogens with or without medroxyprogesterone acetate.

Efficacy for vasomotor symptoms was assessed during the first 12 weeks of treatment in a subset of symptomatic women (n = 241) who had at least 7 moderate to severe hot flushes daily or at least 50 moderate to severe hot flushes during the week before randomization. Premarin (0.3 mg, 0.45 mg, and

0.625 mg tablets) was 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 2 shows the adjusted mean number of hot flushes in the Premarin 0.3 mg, 0.45 mg, and 0.625 mg and placebo treatment groups over the initial 12-week period.

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

Treatment (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 CE (n = 27)				
4	12.29 ± 3.89	1.95 ± 2.77	-10.34 ± 4.73	<0.001
12	12.29 ± 3.89	0.75 ± 1.82	-11.54 ± 4.62	<0.001
0.45 mg CE (n = 32)				
4	12.25 ± 5.04	5.04 ± 5.31	-7.21 ± 4.75	<0.001
12	12.25 ± 5.04	2.32 ± 3.32	-9.93 ± 4.64	<0.001
0.3 mg CE (n = 30)				
4	13.77 ± 4.78	4.65 ± 3.71	-9.12 ± 4.71	<0.001
12	13.77 ± 4.78	2.52 ± 3.23	-11.25 ± 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: Standard errors based on assumption of equal variances.
b: Based on analysis of covariance with treatment as factor and baseline as covariate.

1.2.9 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 Bone Mineral Density.
IN THE 3-YEAR, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED POSTMENOPAUSAL ESTROGEN/PROGESTIN INTERVENTIONS (PEPI) TRIAL, THE EFFECT OF PREMARIN 0.625 MG (CONJUGATED ESTROGENS TABLETS, USP), GIVEN ALONE OR IN COMBINATION WITH MEDROXYPROGESTERONE ACETATE (MPA), ON BONE MINERAL DENSITY (BMD) WAS EVALUATED IN POSTMENOPAUSAL WOMEN. ONE OF THE REGIMENS EVALUATED WAS CONTINUOUS COMBINED PREMARIN 0.625 MG/MPA 2.5 MG, A REGIMEN SIMILAR TO PREMPRO.

Intent-to-treat subjects
In the intent-to-treat subjects, BMD increased significantly ($p<0.001$) compared to baseline or placebo at both the hip and the spine in women assigned to Premarin or the continuous Premarin/MPA regimen. Spinal BMD increased 3.46% among women assigned to Premarin, increased 4.87% in

women assigned to the Premarin/MPA regimen and decreased 1.81% in women assigned to placebo. At the hip, women assigned to Premarin gained 1.31%, women assigned to Premarin/MPA gained 1.94%, while women assigned to placebo lost 1.62%.

Adherent subjects

IN THE ADHERENT SUBJECTS, BMD ALSO INCREASED SIGNIFICANTLY (P<0.001) COMPARED TO BASELINE OR PLACEBO AT BOTH THE HIP AND THE SPINE IN WOMEN ASSIGNED TO PREMARIN OR CONTINUOUS PREMARIN/MPA. SPINAL BMD INCREASED 5.16% AMONG WOMEN ASSIGNED TO PREMARIN, INCREASED 5.49% IN WOMEN ASSIGNED TO PREMARIN/MPA AND DECREASED 2.82% IN WOMEN ASSIGNED TO PLACEBO. AT THE HIP, WOMEN ASSIGNED TO PREMARIN GAINED 2.60%, WOMEN ASSIGNED TO PREMARIN/MPA GAINED 2.23% WHILE WOMEN ASSIGNED TO PLACEBO LOST 2.17%.

These results are summarized in Tables 3 and 4 below.

TABLE 3. MEAN PERCENTAGE CHANGE FROM BASELINE IN BMD AT 36 MONTHS IN INTENT-TO-TREAT SUBJECTS**

Regimen	1.2.9.2 Spine			1.2.9.3 Hip		
	1.2.9.3 n	Mean % Change	95% CI	n	Mean % Change	95% CI
Premarin 0.625 mg	175	+3.46%*†	2.78, 4.14	175	+1.31%*†	0.76, 1.86
Premarin 0.625 mg/ MPA 2.5 mg	174	+4.87%*†	4.21, 5.52	174	+1.94%*†	1.50, 2.39
Placebo	174	-1.81%*	-2.51, -1.12	173	-1.62%*	-2.16, -1.08

* Denotes a statistically significant mean change from baseline at the 0.001 level.

† Denotes mean percentage change from baseline is significantly different from placebo at the 0.001 level.

** INCLUDES ALL 523 WOMEN WHO WERE RANDOMIZED TO EITHER PREMARIN, PREMARIN/MPA OR PLACEBO WHETHER OR NOT THEY COMPLETED THE STUDY. IF BMD WAS NOT AVAILABLE AT 36 MONTHS, THEN THE 12 MONTHS VALUE WAS CARRIED FORWARD AND ANALYZED. BASELINE VALUES WERE CARRIED FORWARD IF 12 MONTHS AND 36 MONTHS DATA WERE UNAVAILABLE. MOST PATIENTS WHO DISCONTINUED STUDY MEDICATION WERE FOLLOWED THROUGH MONTH 36 AND COULD HAVE BEEN OFF THERAPY FOR AN EXTENDED PERIOD PRIOR TO THEIR MONTH 36 EVALUATION.

TABLE 4. MEAN PERCENTAGE CHANGES FROM BASELINE IN BMD AT 36 MONTHS IN ADHERENT SUBJECTS**

Regimen	1.2.9.4 Spine			1.2.9.5 Hip		
	1.2.9.5 n	Mean % Change	95% CI	n	Mean % Change	95% CI
Premarin 0.625 mg	95	+5.16%*†	4.32, 6.00	95	+2.60%*†	1.97, 3.23
Premarin 0.625 mg/ MPA 2.5 mg	144	+5.49%*†	4.79, 6.18	144	+2.23%*†	1.75, 2.71
Placebo	124	-2.82%*	-3.54, -2.10	123	-2.17%*	-2.78, -1.56

* Denotes a statistically significant mean change from baseline at the 0.001 level.

† Denotes mean percentage change from baseline is significantly different from placebo at the 0.001 level.

** Women who completed the study, had BMD reported at month 36, and took 80% or more of their prescribed medication.

IN GENERAL, OLDER WOMEN (55-64 YEARS OF AGE) TAKING PLACEBO IN THE PEPI STUDY LOST BONE AT A LOWER RATE THAN YOUNGER WOMEN (45-54 YEARS OF AGE). CONVERSELY, OLDER WOMEN RECEIVING PREMARIN OR PREMARIN 0.625 MG/MPA 2.5 MG HAD GREATER INCREASES IN BMD THAN YOUNGER WOMEN. TABLES 5 AND 6 PRESENT DATA FOR WOMEN 45 TO 54 YEARS OF AGE AND WOMEN 55 TO 64 YEARS OF AGE.

TABLE 5. MEAN PERCENT CHANGE FROM BASELINE IN BMD FOR WOMEN 45 TO 54 YEARS OF AGE

Regimen	1.2.9.6 Intent-To-Treat Subjects				1.2.9.7 Adherent Subjects			
	1.2.9.7 Mean % Change at the Spine	N	Mean % Change at the Hip		n	Mean % Change at the Spine	n	Mean % Change at the Hip
Premarin 0.625 mg	74	+2.45%†**	74	+1.37%†**	43	+3.73%†**	43	+2.20%†**
Premarin 0.625 mg/ MPA 2.5 mg	69	+3.53%†**	69	+1.26%†**	58	+3.97%†**	58	+1.48%†**
Placebo	78	-2.82%**	78	-2.23%**	50	-4.02%**	50	-3.04%**

** Denotes a statistically significant mean change from baseline at the 0.001 level.
† Denotes the mean percent change from baseline is significantly different from placebo at the 0.001 level.

TABLE 6. MEAN PERCENT CHANGE FROM BASELINE IN BMD FOR WOMEN 55 TO 64 YEARS OF AGE

Regimen	1.2.9.8 Intent-To-Treat Subjects				1.2.9.9 Adherent Subjects			
	1.2.9.9 Mean % Change at the Spine	n	Mean % Change at the Hip		n	Mean % Change at the Spine	n	Mean % Change at the Hip
Premarin 0.625 mg	101	+4.21%†‡**	101	+1.27%†**	52	+6.34%†‡**	52	+2.93%†**
Premarin 0.625 mg/ MPA 2.5 mg	105	+5.75%†‡**	105	+2.39%†**	86	+6.51%†‡**	86	+2.73%†**
Placebo	95	-1.01%*	94	-1.14%*	73	-2.04%‡**	72	-1.60%**

* Denotes a statistically significant mean change from baseline at the 0.05 level.
** Denotes a statistically significant mean change from baseline at the 0.001 level.
† Denotes the mean percent change from baseline is significantly different from placebo at the 0.001 level.
‡ Denotes the mean percent change from baseline in the older age group is significantly different from the mean
percent change in the younger age group at the 0.05 level.

Women's Health Initiative Studies.
The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of Premarin (0.625 mg conjugated equine estrogens per day) alone or the use of Prempro (0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate per day) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD)

(nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of Premarin or Prempro on menopausal symptoms.

The Premarin-only substudy is continuing and results have not been reported. The Prempro substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." Results of the Prempro substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 7 below.

Table 7. RELATIVE AND ABSOLUTE RISK SEEN IN THE PREMPRO SUBSTUDY OF WHI[a]

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

a: Adapted from JAMA, 2002; 288:321-333
b: Includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer
c: A subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes
d: Not included in Global Index
* Nominal confidence intervals unadjusted for multiple looks and multiple comparisons

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

INDICATIONS AND USAGE

Premarin therapy is indicated in the:

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

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

3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.

4. Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.

5. Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).

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

THE MAINSTAYS FOR DECREASING THE RISK OF POSTMENOPAUSAL OSTEOPOROSIS ARE WEIGHT-BEARING EXERCISE, ADEQUATE CALCIUM AND VITAMIN D INTAKE, AND WHEN INDICATED, PHARMACOLOGIC THERAPY. POSTMENOPAUSAL WOMEN REQUIRE AN AVERAGE OF 1500 MG/DAY OF ELEMENTAL CALCIUM. THEREFORE, WHEN NOT CONTRAINDICATED, CALCIUM SUPPLEMENTATION MAY BE HELPFUL FOR WOMEN WITH SUBOPTIMAL DIETARY INTAKE. VITAMIN D SUPPLEMENTATION OF 400-800 IU/DAY MAY ALSO BE REQUIRED TO ENSURE ADEQUATE DAILY INTAKE IN POSTMENOPAUSAL WOMEN.

CONTRAINDICATIONS

Estrogens should not be used in individuals with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.

2. Known, suspected, or history of cancer of the breast except in appropriately selected patients being treated for metastatic disease.

3. Known or suspected estrogen-dependent neoplasia.

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

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

6. Liver dysfunction or disease.

7. Premarin tablets should not be used in patients with known hypersensitivity to their ingredients.

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

WARNINGS

SEE **BOXED WARNINGS.**

The use of unopposed estrogens in women who have a uterus is associated with an increased risk of endometrial cancer.

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

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

a. ***Coronary heart disease and stroke.*** In the Premarin substudy of the Women's Health Initiative study (WHI), an increase in the number of myocardial infarctions and strokes has been observed in women receiving Premarin compared to placebo. These observations are preliminary, and the study is continuing. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

   In the Prempro substudy of WHI, an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving Prempro compared to women receiving placebo (37 vs 30 per 10,000 person-years). The increase in risk was observed in year one and persisted.

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

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

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

b. ***Venous thromboembolism (VTE).*** In the Premarin substudy of the Women's Health Initiative (WHI), an increase in VTE has been observed in women receiving Premarin compared to placebo. These observations are preliminary, and the study is continuing. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In the Prempro substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving Prempro compared to women receiving placebo. The rate of VTE was 34 per 10,000 woman-years in the Prempro group compared to 16 per 10,000 woman-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

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

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

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

In the Premarin substudy of the WHI study, no increased risk of breast cancer in estrogen-treated women compared to placebo was reported after an average of 5.2 years of therapy. These data are preliminary and that substudy of WHI is continuing.

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

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

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

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

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

PRECAUTIONS

A. General

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

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

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

3. ***Hypertriglyceridemia.***
In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications. In the HOPE

study, the mean percent increase from baseline in serum triglycerides after one year of treatment with Premarin 0.625 mg, 0.45 mg, and 0.3 mg compared with placebo were 34.3, 30.2, 25.1, and 10.7, respectively. After two years of treatment, the mean percent changes were 47.6, 32.5, 19.0, and 5.5, respectively.

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

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

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

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

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

9. ***EXACERBATION OF ENDOMETRIOSIS.***
ENDOMETRIOSIS MAY BE EXACERBATED WITH ADMINISTRATION OF ESTROGENS.

A FEW CASES OF MALIGNANT TRANSFORMATION OF RESIDUAL ENDOMETRIAL IMPLANTS HAVE BEEN REPORTED IN WOMEN TREATED POST-HYSTERECTOMY WITH ESTROGEN-ONLY THERAPY. FOR PATIENTS KNOWN TO HAVE RESIDUAL ENDOMETRIOSIS POST-HYSTERECTOMY, THE ADDITION OF PROGESTIN SHOULD BE CONSIDERED.

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

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

C. Laboratory Tests

Estrogen administration should be initiated at the lowest dose for the treatment of postmenopausal moderate to severe vasomotor symptoms and moderate to severe symptoms of postmenopausal vulvar and vaginal atrophy and then guided by clinical response rather than by serum hormone levels (e.g., estradiol, FSH). Laboratory parameters may be useful in guiding dosage for the treatment of hypoestrogenism due to hypogonadism, castration and primary ovarian failure.

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 ANTIGEN, VIII COAGULANT ACTIVITY, IX, X, XII, VII-X COMPLEX, II-VII-X COMPLEX, AND BETA-THROMBOGLOBULIN; DECREASED LEVELS OF ANTI-FACTOR XA AND ANTITHROMBIN III, DECREASED ANTITHROMBIN III ACTIVITY; INCREASED LEVELS OF FIBRINOGEN AND FIBRINOGEN ACTIVITY; INCREASED PLASMINOGEN ANTIGEN AND ACTIVITY.

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

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

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

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility.

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

F. Pregnancy.

Premarin should not be used during pregnancy. (See **CONTRAINDICATIONS**).

G. Nursing Mothers.

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when Premarin is administered to a nursing woman.

H. Pediatric Use.

ESTROGEN THERAPY HAS BEEN USED FOR THE INDUCTION OF PUBERTY IN ADOLESCENTS WITH SOME FORMS OF PUBERTAL DELAY. SAFETY AND EFFECTIVENESS IN PEDIATRIC PATIENTS HAVE NOT OTHERWISE BEEN ESTABLISHED.

LARGE AND REPEATED DOSES OF ESTROGEN OVER AN EXTENDED TIME PERIOD HAVE BEEN SHOWN TO ACCELERATE EPIPHYSEAL CLOSURE, WHICH COULD RESULT IN SHORT STATURE IF TREATMENT IS INITIATED BEFORE THE COMPLETION OF PHYSIOLOGIC PUBERTY IN NORMALLY DEVELOPING CHILDREN. IF ESTROGEN IS ADMINISTERED TO PATIENTS WHOSE BONE GROWTH IS NOT COMPLETE, PERIODIC MONITORING OF BONE MATURATION AND EFFECTS ON EPIPHYSEAL CENTERS IS RECOMMENDED DURING ESTROGEN ADMINISTRATION.

ESTROGEN TREATMENT OF PREPUBERTAL GIRLS ALSO INDUCES PREMATURE BREAST DEVELOPMENT AND VAGINAL CORNIFICATION, AND MAY INDUCE VAGINAL BLEEDING. IN BOYS, ESTROGEN TREATMENT MAY MODIFY THE NORMAL PUBERTAL PROCESS AND INDUCE GYNECOMASTIA. SEE **INDICATIONS** AND **DOSAGE AND ADMINISTRATION** SECTIONS.

I. Geriatric Use.

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

WITH RESPECT TO EFFICACY IN THE APPROVED INDICATIONS, THERE HAVE NOT BEEN SUFFICIENT NUMBERS OF GERIATRIC PATIENTS INVOLVED IN STUDIES UTILIZING PREMARIN TO DETERMINE WHETHER THOSE OVER 65 YEARS OF AGE DIFFER FROM YOUNGER SUBJECTS IN THEIR RESPONSE TO PREMARIN.

1.2.10 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 TO RATES IN THE CLINICAL TRIALS OF ANOTHER DRUG AND MAY NOT REFLECT THE RATES OBSERVED IN PRACTICE. THE ADVERSE REACTION INFORMATION FROM CLINICAL TRIALS DOES, HOWEVER, PROVIDE A BASIS FOR IDENTIFYING THE ADVERSE EVENTS THAT APPEAR TO BE RELATED TO DRUG USE AND FOR APPROXIMATING RATES.

During the first year of a 2-year clinical trial with 2333 postmenopausal women between 40 and 65 years of age (88% Caucasian), 1012 women were treated with conjugated estrogens and 332 were treated with placebo. Table 8 summarizes adverse events that occurred at a rate of $\geq 5\%$.

TABLE 8. NUMBER (%) OF PATIENTS REPORTING ≥ 5% TREATMENT EMERGENT ADVERSE EVENTS

	--Conjugated Estrogens Treatment Group--			
Body System Adverse event	0.625 mg (n = 348)	0.45 mg (n = 338)	0.3 mg (n = 326)	Placebo (n = 332)
Any adverse event	93%	90%	90%	85%
Body as a Whole				
Abdominal pain	16%	15%	17%	11%
Accidental injury	6%	12%	6%	9%
Asthenia	7%	7%	8%	5%
Back pain	14%	13%	13%	12%
Flu syndrome	11%	11%	10%	11%
Headache	26%	32%	29%	28%
Infection	18%	22%	23%	22%
Pain	17%	18%	20%	18%
Digestive System				
Diarrhea	6%	7%	6%	6%
Dyspepsia	9%	9%	11%	14%
Flatulence	7%	7%	6%	3%
Nausea	9%	6%	6%	9%
Musculoskeletal System				
Arthralgia	14%	12%	7%	12%
Leg cramps	5%	7%	3%	2%
Myalgia	5%	5%	9%	8%
Nervous System				
Depression	7%	8%	5%	7%
Dizziness	5%	6%	4%	5%
Insomnia	6%	7%	7%	10%
Nervousness	3%	5%	2%	2%
Respiratory System				
Cough increased	4%	7%	4%	4%
Pharyngitis	10%	10%	12%	11%
Rhinitis	6%	9%	10%	13%
Sinusitis	6%	11%	7%	7%
Upper respiratory infection	12%	10%	9%	11%
Skin and Appendages				
Pruritus	4%	5%	5%	2%
Urogenital				

TABLE 8. NUMBER (%) OF PATIENTS REPORTING ≥ 5% TREATMENT EMERGENT ADVERSE EVENTS

	--Conjugated Estrogens Treatment Group--			
Body System Adverse event	0.625 mg (n = 348)	0.45 mg (n = 338)	0.3 mg (n = 326)	Placebo (n = 332)
System				
Breast pain	11%	12%	7%	9%
Leukorrhea	5%	7%	4%	3%
Vaginal hemorrhage	14%	4%	2%	0
Vaginal moniliasis	6%	5%	5%	2%
Vaginitis	7%	6%	5%	1%

THE FOLLOWING ADDITIONAL ADVERSE REACTIONS HAVE BEEN REPORTED WITH ESTROGEN AND/OR PROGESTIN THERAPY:

1. Genitourinary system.
CHANGES IN VAGINAL BLEEDING PATTERN AND ABNORMAL WITHDRAWAL BLEEDING OR FLOW; BREAKTHROUGH BLEEDING, SPOTTING, DYSMENORRHEA.
INCREASE IN SIZE OF UTERINE LEIOMYOMATA.
VAGINITIS, INCLUDING VAGINAL CANDIDIASIS.
CHANGE IN AMOUNT OF CERVICAL SECRETION.
CHANGE IN CERVICAL ECTROPION.
Ovarian cancer.
Endometrial hyperplasia.
Endometrial cancer.

2. *Breasts.*
Tenderness, enlargement, pain, 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, vomiting.
Abdominal cramps, bloating.
CHOLESTATIC JAUNDICE.
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
Pruritus, rash.

6. *Eyes.*
RETINAL VASCULAR THROMBOSIS.
Steepening of corneal curvature.
Intolerance to contact lenses.

7. *Central Nervous System.*
Headache.
Migraine.
Dizziness
Mental depression.
Chorea.
Nervousness.
Mood disturbances.
Irritability.
Exacerbation of epilepsy.

8. *Miscellaneous*
Increase or decrease in weight.
Reduced carbohydrate tolerance.
Aggravation of porphyria
Edema.
Arthralgias.
Leg cramps.
Changes in libido
Urticaria, angioedema, anaphylactoid/anaphylactic reactions.
Hypocalcemia.
Exacerbation of asthma.
Increased triglycerides.

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

DOSAGE AND ADMINISTRATION

When estrogen is prescribed for a postmenopausal woman with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as clinically appropriate (e.g., at 3-month to 6-month intervals) to determine if treatment is still necessary (see **BOXED WARNINGS** and **WARNINGS**). For women with 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.

1. For treatment of moderate to severe vasomotor symptoms and/or moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

   PATIENTS SHOULD BE TREATED WITH THE LOWEST EFFECTIVE DOSE. GENERALLY WOMEN SHOULD BE STARTED AT 0.3 MG PREMARIN DAILY. SUBSEQUENT DOSAGE ADJUSTMENT MAY BE MADE BASED UPON THE INDIVIDUAL PATIENT RESPONSE. THIS DOSE SHOULD BE PERIODICALLY REASSESSED BY THE HEALTHCARE PROVIDER.

   Premarin therapy may be given continuously with no interruption in therapy, or in cyclical regimens (regimens such as 25 days on drug followed by five days off drug) as is medically appropriate on an individualized basis.

2. FOR PREVENTION OF POSTMENOPAUSAL OSTEOPOROSIS:

When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should be considered only for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered. Patients should be treated with the lowest effective dose. Generally women should be started at 0.625 mg Premarin daily. Dosage may be adjusted depending on individual clinical and bone mineral density responses. This dose should be periodically reassessed by the healthcare provider.

Premarin therapy may be given continuously with no interruption in therapy, or in cyclical regimens (regimens such as 25 days on drug followed by five days off drug) as is medically appropriate on an individualized basis.

3. For treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure:

   Female hypogonadism—0.3 mg to 0.625 mg daily, administered cyclically (e.g., three weeks on and one week off). Doses are adjusted depending on the severity of symptoms and responsiveness of the endometrium.

   IN CLINICAL STUDIES OF DELAYED PUBERTY DUE TO FEMALE HYPOGONADISM, BREAST DEVELOPMENT WAS INDUCED BY DOSES AS LOW AS 0.15 MG. THE DOSAGE MAY BE GRADUALLY TITRATED UPWARD AT 6 TO 12 MONTH INTERVALS AS NEEDED TO ACHIEVE APPROPRIATE BONE AGE ADVANCEMENT AND EVENTUAL EPIPHYSEAL CLOSURE. CLINICAL STUDIES SUGGEST THAT DOSES OF 0.15 MG, 0.3 MG, AND 0.6 MG ARE ASSOCIATED WITH MEAN RATIOS OF BONE AGE ADVANCEMENT TO CHRONOLOGICAL AGE PROGRESSION ($\Delta BA/\Delta CA$) OF 1.1, 1.5, AND 2.1, RESPECTIVELY. (PREMARIN IN THE DOSE STRENGTH OF 0.15 MG IS NOT AVAILABLE COMMERCIALLY). AVAILABLE DATA SUGGEST THAT CHRONIC DOSING WITH 0.625 MG IS

SUFFICIENT TO INDUCE ARTIFICIAL CYCLIC MENSES WITH SEQUENTIAL PROGESTIN TREATMENT AND TO MAINTAIN BONE MINERAL DENSITY AFTER SKELETAL MATURITY IS ACHIEVED.

Female castration or primary ovarian failure—1.25 mg daily, cyclically. Adjust dosage, upward or downward, according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

4. For treatment of breast cancer, for palliation only, in appropriately selected women and men with metastatic disease:

   Suggested dosage is 10 mg three times daily for a period of at least three months.

5. For treatment of advanced androgen-dependent carcinoma of the prostate, for palliation only:

   1.25 mg to 2.5 mg three times daily. The effectiveness of therapy can be judged by phosphatase determinations as well as by symptomatic improvement of the patient.

HOW SUPPLIED
Premarin (conjugated estrogens tablets, USP)

—Each oval purple tablet contains 2.5 mg, in bottles of 100 (NDC 0046-0865-81) and 1,000 (NDC 0046-0865-91).

—Each oval yellow tablet contains 1.25 mg, in bottles of 100 (NDC 0046-0866-81); 1,000 (NDC 0046-0866-91); and Unit-Dose packages of 100 (NDC 0046-0866-99).

—Each oval white tablet contains 0.9 mg, in bottles of 100 (NDC 0046-0864-81).

—Each oval maroon tablet contains 0.625 mg, in bottles of 100 (NDC 0046-0867-81); 1,000 (NDC 0046-0867-91); and Unit-Dose Packages of 100 (NDC 0046-0867-99).

—EACH OVAL BLUE TABLET CONTAINS 0.45 MG, IN BOTTLES OF 100 (NDC 0046-0936-81); AND UNIT-DOSE PACKAGES OF 100 (NDC 0046-0936-099).

—Each oval green tablet contains 0.3 mg, in bottles of 100 (NDC 0046-0868-81) and 1,000 (NDC 0046-0868-91).

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

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

Dispense in a well-closed container as defined in the USP.

1.2.11 PATIENT INFORMATION

Premarin®
(conjugated estrogens tablets, USP)

READ THIS PATIENT INFORMATION BEFORE YOU START TAKING PREMARIN AND READ WHAT YOU GET EACH TIME YOU REFILL PREMARIN. 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 Premarin (an estrogen mixture)?

- Estrogens increase the chances of getting cancer of the uterus.

  Report any unusual vaginal bleeding right away while you are taking Premarin. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

- Do not use estrogens with or without progestins to prevent heart disease, heart attacks, or strokes.

  Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. You and your healthcare provider should talk regularly about whether you still need treatment with estrogens.

1.2.12 What is Premarin?

PREMARIN IS A MEDICINE THAT CONTAINS A MIXTURE OF ESTROGEN HORMONES.

Premarin 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 develop 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 Premarin.

- **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 Premarin to control these problems.

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

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

Premarin is also used to:

- **treat certain conditions in women before menopause if their ovaries do not make enough estrogen naturally.**

- **ease symptoms of certain cancers that have spread through the body, in men and women.**

1.2.13 Who should not take Premarin?

DO NOT START TAKING PREMARIN 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 have had cancer, talk with your healthcare provider about whether you should take Premarin.

- **had a stroke or heart attack in the past year.**

- **currently have or have had blood clots.**

- **are allergic to Premarin tablets or any of its ingredients.** See the end of this leaflet for a list of all the ingredients in Premarin.

- **think you may be pregnant.**

Tell your healthcare provider:

- **if you are breast feeding.** The hormones in Premarin 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 Premarin works. Premarin 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.

HOW SHOULD I TAKE PREMARIN?

- TAKE ONE PREMARIN TABLET AT THE SAME TIME EACH DAY.

- IF YOU MISS A DOSE, TAKE IT AS SOON AS POSSIBLE. IF IT IS ALMOST TIME FOR YOUR NEXT DOSE, SKIP THE MISSED DOSE AND GO BACK TO YOUR NORMAL SCHEDULE. DO NOT TAKE 2 DOSES AT THE SAME TIME.

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

1.2.14 What are the possible side effects of Premarin?

Less common but serious side effects include:

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

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

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

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

Common side effects include:

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

Other side effects include:

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

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

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

- Talk with your healthcare provider regularly about whether you should continue taking Premarin.
- If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you.
- See your healthcare provider right away if you get vaginal bleeding while taking Premarin.
- 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 for getting heart disease.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 04-782/S-115 & S-130

MEDICAL REVIEW(S)

NDA 4-782/S-115

Date NDA Submitted:	**7/31/00**
Date NDA Received:	**7/31/00**
Review Completed:	**6/18/01**
Review Finalized:	**7/18/01**

Medical Officer's Review
(Original Review)

Sponsor:	**Wyeth-Ayerst Research** **P.O. Box 8299** **Philadelphia, PA 19101-8299**
Drug Name:	
Generic:	**Conjugated Estrogens (CE)**
Trade:	**Premarin®**
Pharmacologic category:	**Estrogen**
Route of Administration:	**Oral**
Dosage Form:	**Tablet**
Strength:	**0.45 mg CE**
Proposed Indications:	**1) Treatment of moderate-to-severe vasomotor symptoms associated with the menopause.** **2) Treatment of vulvar and vaginal atrophy associated with the menopause.**

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendation

From a clinical perspective, the reviewer recommends approval of 0.45 mg Premarin® (conjugated estrogens, USP). The data presented in this supplemental new drug application (sNDA) provides sufficient evidence from one large, controlled clinical trial to support the safety and efficacy of 0.45 mg Premarin® for the treatment of vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause.

II. Summary of Clinical Findings

Overview of the clinical program

Premarin® is an approved oral drug product that contains conjugated estrogens, USP. Five dosage strengths of Premarin® are currently approved: 0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg and 2.5 mg. Premarin® is administered orally for the:

1. Treatment of moderate-to-severe vasomotor symptoms (VMS) associated with the menopause.
2. Treatment of vulvar and vaginal atrophy (VVA).
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
4. Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
5. Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).
6. Prevention of osteoporosis.

Prempro™ and Premphase® are two other approved product marketed by Wyeth-Ayerst Research. Prempro™ and Premphase® contain conjugated estrogens (CE) that are found in Premarin® tablets as well as medroxyprogesterone acetate (MPA), a derivative of progesterone. Prempro™ is administered orally in a daily continuous regimen while Premphase® is administered orally in a sequential regimen (CE alone on days 1-14 and CE/MPA on days 15-28 of a 28-day cycle). Prempro™ and Premphase® are also approved for the treatment of VMS, VVA, and the prevention of osteoporosis. On December 30, 1994, with the initial approval of Prempro™ and Premphase® under NDA 20-303, the Agency requested a Phase 4 commitment to investigate the lowest dose combination of CE/MPA for the prevention of osteoporosis. To meet the Phase 4 commitment, the Sponsor conducted the 24-month, Phase 3 Health and Osteoporosis, Progestin and Estrogen (HOPE) study (Study 0713D2-309-US).

Premarin® 0.45 mg, the dosage strength that is the subject of NDA 4-782/S-115, was investigated in a single, controlled clinical trial in Study 0713D2-309-US under IND 21,696. At the time of this submission, Study 0713D2-309-US was an ongoing, prospective, double-blind, placebo/active drug-controlled clinical trial that randomized 2,805 postmenopausal women between 40 and 65 years of age to one of 8 treatment groups for a 2 year duration of treatment.

The HOPE study investigated 8 treatment groups as summarized below:

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

At the completion of study year 1 of Study 0713D2-309-US, data was analyzed regarding the relief of vasomotor symptoms and vulvar and vaginal atrophy. The data from study year 1 is presented in this sNDA. No data regarding the prevention of osteoporosis is presented in this submission. Year 2 of Study 0713D2-309-US was ongoing at the time of this submission on July 31, 2000.

Efficacy

Overall, the data presented shows that the 0.45 mg CE dosage strength is effective in relieving moderate-to-severe vasomotor symptoms associated with the menopause and vulvar and vaginal atrophy in generally healthy postmenopausal women between 40 and 65 years of age.

The data presented was obtained from a 1-year interim analysis of the 24-month HOPE study. The Division of Reproductive and Urologic Drug Products (DRUDP) concurred with the 1-year interim analysis plan. In year 1 of the HOPE study, a total of 2,673 treated subjects contributed data for analyses (the "basic" study group). Approximately 749 of the 2,673 treated subjects in year one continued for year 2 and comprise the metabolic/osteoporosis "substudy" group.

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

For a VMS indication, the 1995 Hormone Replacement Therapy (HRT) Guidance (and the proposed revised 1995 HRT Guidance) indicates that enrolled subjects should have a minimum of 7 to 8 moderate-to-severe hot flushes per day or 50-60 per week at baseline. In the HOPE study, a total of 241 subjects (9% of the 2,673 treated subjects) presented with 7-8 moderate-to-severe hot flushes per day at baseline (or an average of 50 per week) and are included in the VMS subset. These 241 subjects were equally divided between the 8 treatment groups (range between 27 to 34 subjects per group).

Based on the VMS subset data collected over the initial 12 weeks of the HOPE study (recorded daily number and severity of hot flushes), the 0.45 mg CE dosage strength was effective in reducing both the number and severity of moderate-to-severe hot flushes at weeks 4 and 12, the primary efficacy time points for a VMS indication ($p<0.001$ versus placebo at both time points).

Vaginal maturation index results (obtained from vaginal cytology smears collected at baseline, cycle 6 and cycle 13) in the HOPE study demonstrate a statistically significant estrogenic effect on vulvar and vaginal tissue for the 0.45 mg CE dosage strength. The maturation index represents the proportion of vaginal superficial cells relative to the number of parabasal and intermediate cells. The percentage of vaginal superficial cells increased significantly from baseline values at cycles 6 and 13 ($p<0.001$ at both time points).

Safety

Conjugated estrogens have been used in estrogen replacement therapy since 1942. The risks of use are well known. Overall, the treatment emergent adverse event profile of the 0.45 mg CE dosage strength is similar to that of the currently approved products, Premarin® 0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg, and 2.5 mg.

Safety evaluations and monitoring in the submitted study were adequate and complete for the 2,673 treated subjects. Two deaths from lung cancer were reported during the conduct of the first year of the HOPE study (Subject 30921-0018 treated with 0.3 mg CE alone for 134 days and Subject 30937-0129 treated with 0.45 mg CE/2.5 mg MPA for 217 days). Both of these deaths were considered to be unrelated to use of study medication. No additional deaths were reported in the 4-Month Safety Update (covers the period December 24, 1999 through August 2, 2000) or the Second Safety Update (covers the period August 3, 2000 through April 2, 2001).

The Sponsor's analysis showed no endometrial cancer and a total of 32 cases of endometrial hyperplasia occurring during study year 1, across the 8 treatment groups, in Study 0713D2-309-US. However, two cases of reported endometrial hyperplasia that occurred during study year 1 were reclassified as endometrial cancer by

the clinical review team (the reviewer, a second medical officer [also a board-certified pathologist], and the team leader). The reclassified cases of endometrial cancer are consistent with the proposed revised 1995 HRT Guidance for the reading and classification of endometrial biopsy slides that relies on a majority decision diagnosis (2 of 3 pathologists) or a worst-case scenario diagnosis (if the three pathologists disagree). Subject 30924-0011 (0.3 mg CE alone treatment group) and Subject 30912-0049 (0.45 mg CE/1.5 mg MPA treatment group) were both reclassified as endometrial adenocarcinoma in this review.

The occurrence of one case of endometrial adenocarcinoma in the 0.3 mg CE alone treatment group and one case of endometrial adenocarcinoma in the 0.45 mg CE/1.5 mg MPA treatment group in Study 0713D2-309-US is no higher than that seen in other large, prospective controlled trials. Although the occurrence of endometrial adenocarcinoma is a rare event, zero to one case of endometrial adenocarcinoma has been reported in either estrogen alone or estrogen/progestin treatment groups for other large, controlled HRT clinical trials. No cases of endometrial adenocarcinoma were reported in the 4-Month Safety Update or the Second Safety Update.

Data on the remaining 30 cases of endometrial hyperplasia reported during study year 1 showed 20 cases in the 0.625 mg CE alone treatment group (8.03%, n = 249), 9 cases in the 0.45 mg CE alone treatment group (3.23%, n = 279), and 1 case of endometrial hyperplasia in the 0.3 mg CE/1,5 mg MPA treatment group (0.37%, n = 272). In addition, 14 cases of endometrial hyperplasia were reported in the 4-Month Safety Update and 3 cases of endometrial hyperplasia were reported in the Second Safety Update. Overall, the incidence of abnormal endometrial pathology in Study 0713D2-309-US is low (2.2%, 47 cases of endometrial hyperplasia and 2 cases of endometrial adenocarcinoma in 2,153 evaluable subjects).

Serious adverse events reported in the sNDA submission (across the 8 treatment groups), the 4-Month Safety Update, and the Second Safety Update (inclusive of period study year 1 through April 2, 2001) included 4 cases of arterial thrombosis, 3 venous thromboembolic events, seven cases of cholelithiasis with cholecystectomy, and 13 cases of breast cancer. These types of adverse events are known to occur with estrogen alone and estrogen/progestin combination drug products and, overall, do not represent an increased incidence in a clinical trial of 2,673 treated subjects.

Ten of the 13 reported cases of breast cancer occurred during treatment. Three cases of breast cancer were diagnosed after completion of study medication (range of 9 to 42 months). In one CE alone treatment group (0.3 mg), two cases of breast cancer were reported post-study. The third post-study case of breast cancer was reported in the 0.45 mg CE/1.5 mg MPA treatment group. Two cases of breast cancer were reported in the placebo treatment group. Of the remaining eight cases of breast cancer, two were reported in CE alone groups (0.625 mg and 0.45 mg) and six were reported in CE/MPA combination treatment groups (one each in the 0.625 mg CE/2.5 mg MPA and 0.45 mg CE/1.5 mg MPA treatment groups and four in the 0.3 mg CE/1.5 mg MPA treatment group). These 13 cases of breast cancer are not higher than reported in other large HRT clinical trials.

Headaches (29%), breast pain (15%), abdominal pain (15%), and back pain (13%) were some of the more common treatment emergent adverse events reported in the 1-year interim analysis (n = 781, 396, 400 and 351 of 2,673 treated subjects, respectively). These reported treatment emergent adverse events may be considered expected, and are generally similar to adverse events known to occur during treatment with estrogens and/or progestins.

Ten percent of study subjects (n = 266 of 2,673 treated subjects) discontinued study medication due to an adverse event. This rate of discontinuation due to adverse events is not unusual for a large clinical trial and poses no safety concerns.

Special Populations

Premarin® is indicated for use in postmenopausal women. Premarin® therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay. The safety and effectiveness of Premarin® in pediatric patients have not otherwise been established.

The 0.45 mg CE dosage strength was not studied in women with liver disease, and CE are contraindicated in postmenopausal women with liver dysfunction or disease. No studies were conducted in women with renal impairment in this submission. Premarin® is contraindicated in pregnancy.

In a subgroup analysis by age across all 8 treatment groups (<50, 50 to 59, ≥ 60 years) in year 1 of Study 0713D2-309-US, the percentages of women with endometrial hyperplasia increased with age: 0.45% (2 cases in 446 subjects), 1.37% (20 cases in 1,454 subjects), and 3.56% (9 cases in 253 subjects), respectively. Twenty-nine of the 30 cases of endometrial hyperplasia occurred in CE alone treatment groups. Only one case of endometrial hyperplasia occurred in a CE/MPA combination group (0.3 mg CE/1.5 mg MPA).

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

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

CLINICAL REVIEW

I. Introduction and Background

A. Overview of clinical section of sNDA

Premarin® (conjugated estrogens, USP) was approved on May 8, 1942 for the treatment of vasomotor symptoms, based on a pre-marketing safety evaluation in 228 subjects. Initially, a 1.25 mg dosage strength was approved for the relief of vasomotor symptoms. Currently, five dosage strengths of Premarin® are approved: 0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg and 2.5 mg. Premarin® is administered orally for the:

1. Treatment of moderate-to-severe vasomotor symptoms (VMS) associated with the menopause.
2. Treatment of vulvar and vaginal atrophy (VVA).
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F (326)	0.3	Placebo
G (327)	Placebo	0.3/1.5
H (332)	Placebo	Placebo

Submitted with this application are the results of study year 1 of the HOPE study (the basic study). Data on the efficacy and safety of all eight treatment groups is presented regarding the relief of vasomotor symptoms and vulvar and vagina atrophy, reducing the incidence of estrogen-associated endometrial hyperplasia and cancer, and maintaining an acceptable metabolic profile (the metabolic substudy). At the time of this submission, study year 2 was ongoing in a subset of basic study subjects to examine the efficacy and safety of these regimens in reducing the risk of postmenopausal osteoporosis.

Fifty-seven (57) study sites participate in this prospective, double-blind, randomized, placebo/active drug-controlled study. One study site, [redacted] (n=51 substudy subjects), was terminated due to non-compliance with Good Clinical Practice. No data from this study site is included in efficacy analyses.

B. Hormone replacement therapy symptomatic indications

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

For products intended to treat vulvar and vaginal atrophy, prestudy and end-of-study lateral wall vaginal cytology smears are collected to determine the percentages of parabasal, intermediate and superficial cells (vaginal maturation index). In addition, the Division strongly recommends that studies assess physician signs and subject self-assessment of symptoms at baseline and at end-of-study (instituted in 1999). The physician assessment of signs includes the following categories: vaginal atrophy, vaginal pallor, vaginal dryness, vaginal friability, and vaginal petechiae. The subject's self-assessment of vaginal symptoms include the following categories: vaginal dryness, vaginal irritation/itching, difficulty passing urine, urinary leakage, pain during intercourse, pain after intercourse, and bleeding after intercourse.

C. Important milestones in product development

Premarin® (1.25 mg conjugated estrogens) was approved in 1942 for the relief of vasomotor symptoms. In 1972, the Federal Register Drug Efficacy Study Implementation Notice (DESI 1543, 37 FR 14826 dated July 31, 1972), which was based on the National Academy of Sciences-National Research Council Drug Efficacy Study Group (NAS-NRC) review of published literature, found non-contraceptive estrogen drugs (including Premarin®) effective for several "DESI Indications". This 1972 notice and two additional notices (DESI 1543, 41 FR 43114 dated September 29, 1976 and 51 FR 12568 dated April 11, 1986) defined these "DESI Indications" as follows: moderate-to-severe vasomotor symptoms (MSVS) associated with the menopause, senile vaginitis, kraurosis vulvae, pruritis vulvae, abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, female hypogonadism, amenorrhea, female castration, primary ovarian failure, prevention of postpartum breast engorgement, palliation of selected cases of inoperable progressing mammary and prostatic carcinoma, and postmenopausal osteoporosis.

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

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

In 1994, the FDA approved NDA 20-303 for Premarin® (0.625 mg) plus Cycrin® brand of medroxyprogesterone acetate (MPA, 2.5 mg and 5 mg) in women with intact uteri for the treatment of vasomotor symptoms associated with the menopause, the treatment of vulvar and vaginal atrophy, and the prevention of osteoporosis. Initially, Prempro™ and Premphase® were co-packaged as two separate tablets. However, in 1995 the FDA approved NDA 20-527 for CE/MPA as a single combination tablet (conjugated estrogens tablet core with a thin coating containing MPA).

The Phase 4 study protocol for Study 0713D2-309-US was designed in accordance with the March 20, 1995 FDA HRT Guidance and the November 19, 1997 Committee for Proprietary Medicinal Products (CPMP), "Points to Consider on Hormone Replacement Therapy" publication. The trial length, use of washout periods, inclusion criteria, measurements of hot flushes and endometrial hyperplasia endpoints were conducted as recommended in these documents.

As previously stated, Study 0713D2-309-US was undertaken to satisfy a post-approval commitment to the Agency to determine the lowest effective dose of CE/MPA for the prevention of osteoporosis in women with a

uterus. The 1995 HRT Guidance specifies a comparison of three doses of CE/MPA to evaluate osteoporosis prevention, as well as a comparison of unopposed CE treatments to evaluate endometrial protection. A placebo group was included for comparison in the analyses of VMS, VVA, and bone mineral density (BMD) assessments. The following 8 treatment groups were included in the HOPE study:

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

D. Foreign marketing status

Premarin® is currently approved in 89 countries worldwide. Premarin® has not been withdrawn or suspended for safety reasons in any country.

E. Other pharmacologically related agents

Premarin®, derived from the urine of pregnant mares, is the only "natural" oral conjugated estrogens drug product. One oral synthetic conjugated estrogens drug product, Cenestin® (synthetic conjugated estrogens, A), was approved for marketing in the US for HRT on March 24, 1999. Six estradiol transdermal systems are approved for market use in the US for HRT (Estraderm®, Vivelle®, Vivelle-Dot®, Climara®, Alora®, and Esclim®). One conjugated estrogens IV injection (Premarin® IV), one conjugated estrogens vaginal cream (Premarin® Vaginal Cream), one estradiol vaginal tablet (Vagifem®), and one estradiol vaginal ring (Estring®) are also approved for market use in the US for HRT. In addition, five estrogen/progestin combination tablets for oral administration (Prempro™, Premphase®, Activella™, femhrt®, and Ortho-Prefest®) and one estrogen/progestin transdermal system (Combipatch™) are also approved for market use in the US for HRT.

II. Clinically relevant findings from chemistry, toxicology, microbiology, or biopharmaceutics reviews

A. Chemistry, Manufacturing and Controls

The conjugated estrogens found in Premarin® Tablets are a mixture of more than 10 estrogens derived from pregnant mares' urine including the sodium sulfate conjugates of estrone, equilin, 17α-dihydroequilin, 17β-dihydroequilin, 17α-estradiol, 17β-estradiol, equilenin, 17α-dihydroequilenin, 17β- dihydroequilenin, and $\Delta^{8,9}$-dehydroestrone.

The CE dosage form consists of a core tablet containing CE, which is [ ] [ ] The quantitative composition of the [ ] tablet core for the 0.45 mg tablet differs from the approved 0.3 mg and 0.625 mg tablets only in the input of [ ] (active ingredient) and [ ] (inactive ingredient), which are adjusted to maintain constant tablet weight among the 0.3 mg, 0.45 mg and 0.625 mg dosage strengths.

A 24-month expiration dating period is proposed for the 0.45 mg CE tablet when stored at 25° C. Proposed packaging includes tablets in push-through/peel-seal blister cards and [ ]

Please refer to the Chemistry, Manufacturing and Controls Review.

B. Pharmacology and Toxicology

Please refer to the Pharmacology Review.

III. Human pharmacokinetics and pharmacodynamics

A. Pharmacokinetics

The pharmacokinetics of 0.45 mg CE was examined in a single bioavailability study in 31 postmenopausal women. In Study 0713D2-119-US, the comparative bioavailabilities for Premarin® components and MPA were evaluated following administration of two tablets of 0.625 mg CE/2.5 mg MPA (treatment A), two tablets of 0.45 mg CE/2.5 mg MPA (treatment B), 0.45 mg CE/1.5 mg MPA (treatment C), and two tablets of 0.45 mg CE alone (treatment D).

The results of this PK study showed that two tablets of 0.45 mg CE/2.5 mg MPA (treatment B), 0.45 mg CE/1.5 mg MPA (treatment C), or 0.45 mg CE (treatment D) tablets produced lower estrogen concentrations than two tablets of 0.625 mg CE/2.5 mg MPA (treatment A). The estrogen ratios of mean C_{max} observed following treatments of B, C, and D to mean C_{max} for treatment A ranged from 56% to 76%, and the ratios of mean AUC ranged from 57% to 84%.

These results show that CE and MPA behaved pharmacokinetically in a dose-proportional manner, and MPA had no effect on the pharmacokinetics of CE.

B. Pharmacodynamics

Although the 0.45 mg CE formulation used in the clinical study was identical to the to-be-marketed formulation in terms of scale of manufacture and composition, they differed in color coat. The clinical formulation was white. The to-be-marketed color coat is blue. However, the Clinical and Biopharmaceutics Review indicates that the dissolution profiles between the clinical batch and the market batch appear to be similar for the 0.45 mg CE tablet despite the color change.

Please see the Clinical Pharmacology and Pharmacokinetics Review.

IV. Description of clinical data and sources

A. Overall data

In sNDA 4-782/S-115, the clinical development program consisted of one Phase 1 study (Study 0713D2-119-US) and one large multicenter Phase 3 study (Study 0713D2-309-US) conducted in the US. The Phase I study was designed to describe the pharmacokinetics of the 0.45 mg CE alone dose and two lower dose combination products (0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA). The Phase 3 study was designed to evaluate whether the 0.45 mg CE dose (intermediate dose to the approved 0.3 mg and 0.625 mg CE doses) would be effective in relieving VMS, and whether a lower dose of CE or CE/MPA (than the approved 0.625 mg Premarin® or Prempro™ 2.5, respectively) would have an impact on bone mineral density over a two-year period. This 2-year Phase 3 study is comprised of a basic study (year 1, total of 2,673 treated women), and a metabolic/osteoporosis substudy (years 1 and 2, approximately 749 of the 2,673 treated women in substudy).

Completed study year 1, analyzed and presented in this application, contains final data on 2,673 treated subjects (including the ≅ 749 substudy subjects) for endometrial safety, control of vasomotor symptoms, vaginal maturation index, and metabolic parameters (substudy subjects). An interim analysis of bone mineral density and bone-related metabolic parameters is not presented in this year 1 interim analysis. Year 2 of Study 0713D2-309-US was ongoing for the substudy population at the time of this submission.

The protocol for Study 0713D2-309-US, originally submitted on January 13, 1994 and finalized on July 18, 1995, was amended on February 23, 1999. This amendment specified that an interim analyses of data by treatment group, but not individual subject data, would be provided confidentially to individuals at the National Institutes of Health (NIH) for subjects assigned to treatment after August 23, 1995 through July 31, 1998. Prestudy and cycle 6 data, reported as either mean percent change from baseline or mean change from baseline, was provided for the following parameters:

- high density lipoprotein cholesterol (HDL-C)
- HDL_2-C
- Low-density lipoprotein cholesterol (LDL-C)
- lipoprotein (LP) (a)

- fibrinogen activity
- factor VIII activity
- antithrombin III activity
- plasminogen activator inhibitor-1 (PAI-1) antigen

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

In a December 9, 1999 submission to IND 21,696, an unblinding strategy was devised in order to assemble and analyze interim data for this sNDA and to preserve the integrity of the ongoing HOPE substudy (see sNDA 4-782, Addendum 2, Unblinding Procedures for Interim Analysis of HOPE Study, Volume 30, pages 285-289). The Division concurred with the proposed unblinding procedures on December 16, 1999.

B. Listing of clinical trials

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

Table 1: Supplemental NDA 4-782 Clinical Development Program

Protocol No.	Study Design Status of Study	Treatment Group And Dose (mg)	Number of Treated Subjects
0713D2-119-US	Completed, single-dose, 4-period, 4-treatment, crossover design Phase 1 study of the comparative bioavailability of conjugated estrogens and medroxyprogesterone acetate	CE/MPA Group A: 2 x 0.625 mg/2.5 mg Group B: 2 x 0.45 mg/2.5 mg Group C: 2 x 0.45 mg/1.5 mg CE alone Group D: 2 x 0.45 mg	31
0713D2-309-US	Interim 1-year prospective, double-blind, randomized, Phase 3 study of multiple doses of conjugated estrogens and conjugated estrogens plus medroxyprogesterone acetate in postmenopausal women	Group A: 0.625 mg CE Group B: 0.625 mg CE/2.5 mg MPA Group C: 0.45 mg CE Group D: 0.45 mg CE/2.5 mg MPA Group E: 0.45 mg CE/1.5 mg MPA Group F: 0.3 mg CE Group G: 0.3 mgCE/1.5 mg MPA Group H: Placebo	348 331 338 340 331 326 327 332
0713D2-309-US	Ongoing, 2-year prospective, double-blind, randomized, Phase 3 substudy of multiple doses of conjugated estrogens and conjugated estrogen plus medroxyprogesterone acetate in postmenopausal women	Group A: 0.625 mg CE Group B: 0.625 mg CE/2.5 mg MPA Group C: 0.45 mg CE Group D: 0.45 mg CE/2.5 mg MPA Group E: 0.45 mg CE/1.5 mg MPA Group F: 0.3 mg CE Group G: 0.3 mgCE/1.5 mg MPA Group H: Placebo	≅ 749 subjects, approx. 93 per group

Source: Adapted from sNDA 4-782, Volume 3, pages 55-57.

C. Postmarketing experience

The 0.45 mg CE alone dosage strength is not currently approved in the US or in any foreign country.

D. Literature review

References are provided in the submission that pertain, primarily, to the currently approved Premarin® dosage strengths and indications. Two additional references provide data regarding low-dose CE, supplemented with calcium use, and inhibition of bone resorption. No additional FDA literature review was conducted.

V. Clinical Review Methods

A. How review was conducted

Data from one pharmacokinetic Phase 1 study (Study 0713D2-119-US), and a single Phase 3 clinical trial (Study 0713D2-309-US) were reviewed separately. Safety data from the HOPE study submitted in the 4-Month Safety Update (dated November 30, 2000) and in the Second Safety Update (dated May 15, 2001) were reviewed upon receipt.

B. Overview of materials consulted in review.

IND 21,696/S-122 dated July 18, 1995, initial submission of Protocol 0713D2-309-US, was reviewed in detail.

C. Overview of methods used to evaluate data quality and integrity

No DSI audit was requested. Premarin® (conjugated estrogens) is an approved drug and longstanding efficacy and safety data are available for Premarin®. Based on extensive clinical experience with the approved higher dosage strengths of Premarin® for the treatment of VMS and VVA, it was determined that this sNDA had no specific safety concerns and did not require inspection.

D. Informed consent and standard of patient care

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

E. Financial disclosure evaluation

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

VI. Review of Efficacy

A. Conclusions

The data presented in this supplemental new drug application provides sufficient evidence from one large, controlled clinical trial to support the safety and efficacy of 0.45 mg conjugated estrogens for the treatment of vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause.

In the DOSAGE AND ADMINISTRATION section of the submitted labeling, the Sponsor proposed the following language for the treatment of vasomotor symptoms: [ ]

B. General approach to review of the efficacy of the drug

Data from one pharmacokinetic Phase 1 study (Study 0713D2-119-US), and a single Phase 3 clinical trial (Study 0713D2-309-US) were reviewed in detail. On November 30, 2000, the Sponsor submitted a 4-Month Safety Update. This safety update summarizes all relevant safety data from the HOPE study from December 23, 1999 (the cutoff date for the 1-year sNDA) to August 2, 2000. On May 15, 2001, the Sponsor submitted the Second Safety Update which summarizes all relevant safety data from the HOPE study that were on the database starting August 3, 2000 and continuing through April 2, 2001. The submitted safety updates were reviewed in detail.

C. Detailed review of Study 0713D2-309-US by indication

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

Group	CE (mg)	CE/MPA (mg)
A	0.625	Placebo
B	Placebo	0.625/2.5
C	0.45	Placebo
D	Placebo	0.45/2.5
E	Placebo	0.45/1.5
F	0.3	Placebo
G	Placebo	0.3/1.5
H	Placebo	Placebo

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

Effects on Vasomotor symptoms

For the basic study, the Sponsor indicated that, "every effort was made to recruit patients who experienced an average of at least 7 to 8 moderate to severe hot flushes per day." However, relatively few of the basic study subjects met this criterion. Of the 2,805 study subjects randomized, 2,673 received study medication and appear in the study analyses; 132 subjects do not appear in the analyses (81 randomized subjects provided no medication use information and 51 subjects participated at Study Site 30952 that was terminated related to noncompliance with Good Clinical Practice). These 2,673 treated subjects were equally divided across the 8 treatment groups. Subject numbers per group were similar and ranged between 331 and 348 subjects per treatment group.

However, only 9% of treated subjects (241 of 2,673 subjects) met the inclusion criterion of 7-8 MSVS per day or 50 per week at baseline (VMS subset). These 241 subjects were, similarly, equally divided between the 8 treatment groups (range between 27 to 34 subjects per group).

Vasomotor symptoms were assessed by evaluation of the subject's daily diary for reports of hot flushes. Per the study protocol, at least 5 of 7 days of diary data had to be available for an on-treatment week to be included in the analysis. The adjusted mean daily number of hot flushes was calculated as the sum of the number of hot flushes on each day/number of days for which data were available. Weeks 1 through 12 were assessed. However, no procedure for carrying forward missing data was implemented. The comparison to placebo was performed on the observed number and severity of hot flushes with baseline as a covariate, rather than change from baseline.

The average daily severity score was calculated as the sum of the daily severity scores/number of days for which data were available. The daily severity score was calculated as follows:

> [(the number of mild hot flushes) x 1 + (the number of moderate hot flushes) x 2 + (the number of severe hot flushes) x 3]/the total number of hot flushes on that day.

Utilizing the VMS subset population, vasomotor symptoms were analyzed in both modified intent-to-treat (modified ITT, by cycle) and efficacy evaluable (EE, by week and by cycle) subject populations. Per the application, the modified ITT subject population included all subjects randomly assigned who recorded taking study medication who had at least one baseline hot flush recorded in the last 7 days of screening before study medication. The EE subject population included all subjects randomly assigned who recorded taking study medication and who had at least 7 moderate-to-severe baseline hot flushes on each of the last 7 days of screening, or at least 50 total hot flushes on the last 7 days combined.

Reviewer's Comments

The modified ITT population by cycle, as defined in the submission, does not meet the HRT Guidance for either the entry criteria or the recommended analysis for a VMS indication. The proposed revised 1995 HRT Guidance states, "Entry criteria for the indication of moderate-to-severe vasomotor symptoms should require enrolled subjects to have a minimum of 7 to 8 moderate-to-severe hot flushes per day, or 50 to 60 per week at baseline." In addition, the proposed revised 1995 HRT Guidance states, " For estrogen products intended to treat moderate-to-severe vasomotor symptoms, the primary efficacy analysis should show both a clinically and a statistically significant reduction in the frequency and severity of hot flushes in the treated groups compared with the control groups. This reduction should occur within 4 weeks of initiation of treatment and should be maintained throughout 12 weeks of treatment." Therefore, the submitted modified ITT population analysis by cycle will not be considered in this review. Likewise, the proposed EE population analysis by cycle will also not be considered in this review.

The submitted EE population analysis by week, however, does meet the HRT Guidance because it includes:

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

The reviewer more commonly refers to the Sponsor's "EE population" as the ITT population.

In other NDAs submitted for a vasomotor symptoms indication, efficacy analyses have utilized the mean number of hot flushes at baseline (the calculated mean of hot flushes over the seven day period preceding the start of study drug) and not the adjusted mean as calculated in the submission. The ITT population analysis with last observation carried forward (LOCF) approach is most commonly utilized. In addition, the Division has required analyses of the mean change in the number of hot flushes between baseline and on-treatment weeks 4, 8, and 12 as compared to placebo. This data is represented in tabular form demonstrating the baseline mean number of moderate-to-severe hot flushes and the mean number of hot flushes and mean change in hot flushes at weeks 4, 8 and 12.

For consistency in labeling, the Sponsor was requested to prepare frequency and severity tables of the ITT subset population (i.e., 7-8 moderate-to-severe hot flushes at baseline) with LOCF approach showing the calculated baseline, week 4, week 8, and week 12 mean number and severity of hot flushes per treatment group and the mean change from baseline in number and severity at weeks 4, 8, and 12 as compared to placebo. The tables should also include a p-value versus placebo for weeks 4, 8, and 12.

The Sponsor complied with the Division's request on March 15, 2001. Two tables were provided that represent the mean values and comparisons between the active treatment groups and placebo (at weeks 4, 8, and 12) for the number and severity of hot flushes in subjects with at least 7 moderate-to-severe hot

flushes per day or at least 50 per week at baseline. Missing data was imputed using a last observation carried forward approach as was requested by the Division.

As shown in Table 2, the 0.45 mg CE alone treatment group is effective in reducing the number of moderate-to-severe hot flushes at weeks 4, 8, and 12 as compared to placebo ($p<0.001$ at all time points). See Supportive Table 1 in Appendix A of this review for the change in the mean number of moderate-to-severe hot flushes during treatment for all 8 treatment groups in Study 0713D2-309-US.

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

Week	Group C 0.45 mg CE[a] N = 32 of 338 (9%)	Group H Placebo N = 28 of 332 (8%)
Baseline		
Mean Number	12.25	11.69
Week 4		
Mean Number	5.07	8.09
Mean Change[b]	-7.21	-3.80
p-value vs. Placebo[c]	<0.001	NA
Week 8		
Mean Number	2.84	6.93
Mean Change[b]	-9.41	-4.86
p-value vs. Placebo[c]	<0.001	NA
Week 12		
Mean Number	2.33	5.81
Mean Change[b]	-9.93	-5.98
p-value vs. Placebo[c]	<0.001	NA

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

Table 3 shows the analyses of the change from baseline in the mean severity of hot flushes for weeks 4, 8, and 12. The 0.45 mg CE treatment group is effective in reducing the severity of hot flushes at all time points ($p<0.001$ at all time points). See Supportive Table 2 in Appendix A of this review for the change in the mean severity of moderate-to-severe hot flushes during treatment for all 8 treatment groups in the HOPE study.

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

Week	Group c 0.45 mg CE[a] N = 32 of 338 (9%)	Group H Placebo N = 28 of 332 (8%)
Baseline		
Mean Severity	2.23	2.37
Week 4		
Mean Severity	1.34	2.03
Mean Change[b]	-0.97	-0.29
p-value vs. Placebo	<0.001	NA
Week 8		
Mean Severity	0.98	1.76
Mean Change[b]	-1.33	-0.57
p-value vs. Placebo	<0.001	NA
Week 12		
Mean Severity	0.85	1.62
Mean Change[b]	-1.47	-0.72
p-value vs. Placebo	<0.001	NA

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

One interesting observation across the three CE alone treatment groups (0.625 mg, 0.45 mg, and 0.3 mg) results from the Sponsor's subgroup analysis of VMS by age in subjects who completed 12 treatment weeks (this is not the ITT population the reviewer used to evaluate efficacy). Although the demographics and baseline characteristics for the VMS subset were not evaluated in the submission, supportive tables in the submission show that the majority of the VMS subset subjects who completed 12 treatment weeks were in the 50 to 59 age group with less in the < 50 age group and even fewer in the ≥ 60 age group. While the age subgroup numbers are too small to permit conclusions, they show interesting differences in treatment effect. Results by age group (< 50, 50 to 59, ≥ 60 years of age) demonstrate an irregular treatment effect in reducing the frequency and severity of hot flushes, particularly in women < 50 years of age and in women 50 to 59 years of age. In the submission, the ≥ 60 years of age subgroup had too few women to permit an observational assessment of treatment effect.

For frequency, the 0.625 mg CE dosage strength demonstrated a consistent statistically significance reduction in hot flush frequency at all time points ($p<0.001$ at weeks 4, 8, and 12) in both subgroups (< 50 and 50 to 59 years of age). Likewise, the 0.45 mg and 0.30 mg CE dosage strengths demonstrated a consistent statistically significance reduction in hot flush frequency at all time points, but only in the 50 to 59 years of age subgroup (p-values ranged from $p<0.001$ to $p=0.028$). In the < 50 years of age subgroup, the 0.45 mg and 0.3 mg CE alone dosage strengths showed a delayed reduction in hot flush frequency to week 8 ($p=0.053$ at week 4 and $p=0.014$ at week 8 for the 0.45 mg CE group; $p=0.057$ at week 4 and $p=0.007$ at week 8 for the 0.3 mg CE group). The reductions shown at week 8 for the 0.45 mg CE and 0.3 mg CE dosage strengths were sustained through week 12 ($p=0.026$ and $p=0.004$, respectively).

For severity, the 0.625 mg CE dosage strength demonstrated a consistent statistically significance reduction in hot flush severity at weeks 4, 8, and 12 in both the < 50 and 50 to 59 years of age subgroups (p-values ranged from $p<0.001$ to $p=0.014$). However, results of the age group analyses for severity (women < 50 years of age compared to women 50 to 59 years of age) are more variable for the 0.45 mg and 0.3 mg CE dosage strengths. The 0.45 mg CE dosage strength reduced severity in both of these age subgroups at weeks 4 and 8 but not at week 12 ($p=0.67$ at week 12 for the < 50 years of age group and $p=0.11$ at week 12 for the 50 to 59 age group). On the other hand, the 0.3 mg CE alone dosage strength showed a delayed treatment effect for severity in both age subgroups ($p=0.097$ at week 4 and $p=0.028$ at week 8 in the < 50 subgroup; $p= 0.087$ at week 4 and $p=0.044$ at week 8 for the 50 to 59 years of age subgroup). More data is needed to clarify these observations in the ITT population.

Vaginal maturation index

A vaginal cytological smear was obtained at the prestudy visit and during cycles 6 and 13 to determine the vaginal maturation index (VMI). A VMI was reported as the proportion of vaginal superficial cells, relative to the number of parabasal and intermediate cells, in a lateral vaginal wall smear. VMI data was analyzed within treatment groups by the change from baseline using the Wilcoxon matched pairs signed-rank test and among groups using Wilcoxon's rank-sum test. However, data in the submission represented median rather than mean change from baseline. Upon request, the Sponsor provided data demonstrating the mean change from baseline at cycle 6 and cycle 13 on March 22, 2001. See Table 4.

The VMI results show that the percentages of vaginal superficial cells increased significantly from screening values at cycles 6 and 13, and the differences were statistically significant from placebo for the 0.45 mg dosage strength ($p<0.001$). See Supportive Table 3 in Appendix A of this review for a summary of maturation index results for all 8 treatment groups in Study 0713D2-309-US.

Table 4: Subjects with Maturation Index Results, Mean Value and Comparison Between the 0.45 mg CE Alone Group and the Placebo Group by Cycle, Intent-to-Treat Population with LOCF

Treatment[a] (N) Type of Cell	Percentage of Epithelial Cells (%)			
	Baseline Mean ± SE	Cycle 6 Mean Change ± SE	Cycle 13 Mean Change ± SE	p-Value vs. Placebo[b] Cycle 6 – Cycle 13
Group C (n = 322) 0.45 mg CE				
Superficial Cells	7.9 ± 0.8	12.7 ± 1.0	12.9 ± 1.0	<0.001 - <0.001
Intermediate Cells	54.7 ± 2.0	14.3 ± 2.0	16.6 ± 2.1	<0.001 - <0.001
Parabasal Cells	34.3 ± 2.2	-27.0 ± 2.2	-29.5 ± 2.2	<0.001 - <0.001
Group H (n = 321) Placebo				
Superficial Cells	6.8 ± 0.6	0.8 ± 1.0	0.7 ± 1.0	<0.001 - <0.001
Intermediate Cells	56.8 ± 2.1	-3.2 ± 2.0	-3.1 ± 2.1	<0.001 - <0.001
Parabasal Cells	36.5 ± 2.3	2.4 ± 2.2	2.3 ± 2.2	<0.001 - <0.001

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

D. Efficacy conclusions

Data from a total of 2,673 subjects in Study 0713D2-309-US (HOPE study 1-year interim analysis) was presented in this submission. In the submission, two indications were sought for the 0.45 mg CE alone dosage strength, the treatment of moderate-to-severe vasomotor symptoms and the treatment of vulvar and vaginal atrophy.

Although the HOPE study inclusion criteria proposed to enroll postmenopausal women with 7-8 moderate-to-severe hot flushes per day for the treatment of vasomotor symptoms indication, only a subset of 241 subjects met this inclusion criterion. As such, efficacy data presented represented only 9% of the total study population. Nonetheless, the data presented from the 1-year interim analysis of Study 0713D2-309-US (0.45 mg CE alone dosage strength versus placebo) shows that the 0.45 mg CE alone dosage strength is effective in relieving moderate-to-severe hot flushes and vulvar and vaginal atrophy in postmenopausal women.

The Statistical Review and Evaluation Review, dated March 18, 2001, concurs that the results from the HOPE study show a significantly lower number and severity of hot flushes in all active treatment groups compared with the placebo group, and that these differences are significant at weeks 4, 8, and 12. Please refer to the Statistical Review and Evaluation Review.

VII. Review of Safety

A. Safety conclusions

Data presented in the 1-year interim analyses of Study 0713D2-309-US shows that the overall safety profile of the 0.45 mg CE dosage strength is similar to that of the approved 0.3 mg and 0.625 mg Premarin® tablets. In addition, the 0.45 mg CE dosage strength demonstrated a lower incidence of vaginal bleeding and spotting (14% versus 4%), and a lower incidence of endometrial hyperplasia (8.03% versus 3.23%) compared with the approved 0.625 mg CE dosage strength.

B. Description of subject exposure

One thousand twelve (1,012) subjects of the 2,673 treated subjects in the Phase 3 clinical study were exposed to at least one dose of CE alone and 1,329 subjects were exposed to at least one dose of CE/MPA. A total of 332 subjects received placebo tablets. Table 5 shows the number of subjects exposed to each of the 7 active treatment groups in the HOPE study.

Table 5: Assessments of Exposure[a] to Active Medication

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

Source: Adapted form sNDA 4-782, Volume30, Table 10.1A, page 134.
[a] Values represent the maximum possible exposure to study medication.
[b] mg of CE or CE/MPA.

Study demographics

The treatment groups were comparable in all demographics and baseline characteristics. See Table 6. Approximately 26-30% of treated subjects in each of the 8 treatment groups were participants in the year 2 substudy. The majority of study subjects are Caucasian (88%, 2,358 of 2,673 treated subjects). Other demographic characteristics, such as height, weight, and body mass index are comparable across treatment groups. The mean age at menopause is 48.6 (SD of 4.3) and is comparable across groups. Study participants have a mean of 4.7 years since menopause (range of 4.4 to 5.0 years across treatment groups).

Table 6: Demographic and Baseline Characteristics by Treatment Group

Treatment Group mg dose[a] (n)	Characteristic					
	Substudy subject n (%)	Age (years)	Ethnic origin n (%)	Body mass index (kg/m^2)	Age at menopause (years)	Years since menopause (years)
Group A 0.625 (n = 348)	No = 251 (72) Yes = 97 (28)	Mean = 53.2 SD = 4.8	White = 316 (91) Black = 16 (5) Hispanic = 11 (3) Other = 5 (1)	Mean = 24.8 SD = 2.7	Mean = 48.8 SD = 4.3	Mean = 4.4 SD = 4.0
Group B 0.625/2.5 (n = 331)	No = 245 (74) Yes = 86 (26)	Mean = 53.4 SD = 4.8	White = 291 (88) Black = 17 (5) Hispanic = 11 (3) Other = 12 (4)	Mean = 24.3 SD = 2.8	Mean = 48.6 SD = 4.6	Mean = 4.8 SD = 4.8
Group C 0.45 (n = 338)	No = 243 (72) Yes = 95 (28)	Mean = 53.4 SD = 4.8	White = 290 (86) Black = 24 (7) Hispanic = 18 (5) Other = 6 (2)	Mean = 24.2 SD = 2.7	Mean = 48.4 SD = 4.2	Mean = 5.0 SD = 4.4
Group D 0.45/2.5 (n = 340)	No = 244 (72) Yes = 96 (28)	Mean = 53.5 SD = 5.1	White = 308 (91) Black = 16 (5) Hispanic = 6 (2) Other = 10 (3)	Mean = 24.5 SD = 2.7	Mean = 48.6 SD = 4.5	Mean = 4.9 SD = 4.0
Group E 0.45/1.5 (n = 331)	No = 237 (72) Yes = 94 (28)	Mean = 53.1 SD = 4.8	White = 290 (88) Black = 20 (6) Hispanic = 15 (5) Other =6 (2)	Mean = 24.4 SD = 2.7	Mean = 48.4 SD = 4.3	Mean = 4.8 SD = 4.1
Group F 0.3 (n = 326)	No = 237 (73) Yes = 89 (27)	Mean = 53.8 SD = 4.9	White = 285 (87) Black = 19 (6) Hispanic = 16 (5) Other = 6 (2)	Mean = 24.6 SD = 2.8	Mean = 49.0 SD = 4.3	Mean = 4.8 SD = 4.4
Group G 0.3/1.5 (n = 327)	No = 229 (70) Yes = 98 (30)	Mean = 53.5 SD = 4.8	White = 288 (88) Black = 21 (6) Hispanic = 11 (3) Other = 7 (2)	Mean = 24.6 SD = 2.8	Mean = 48.7 SD = 4.3	Mean = 4.7 SD = 4.4

Group H Placebo (n = 332)	No = 238 (72) Yes = 94 (28)	Mean = 52.9 SD = 4.8	White = 290 (87) Black = 19 (6) Hispanic = 13 (4) Other = 10 (3)	Mean = 24.3 SD = 2.8	Mean = 48.5 SD = 4.0	Mean = 4.4 SD = 3.7
Total (n = 2673)	No = 1924 (72) Yes = 749 (28)	Mean = 53.3 SD = 4.9	White =2,358 (88) Black = 152 (6) Hispanic = 101 (4) Other = 62 (2)	Mean = 24.4 SD = 2.8	Mean = 48.6 SD = 4.3	Mean = 4.7 SD = 4.2

Source: Adapted from sNDA 4-782, Volume 30, Table 8.2A, pages 82-83.
[a] mg dose of CE or CE/MPA
SD = standard deviation.

C. Methods and Specific Findings of Safety Review

Deaths
Two (2) deaths were reported during Study 0713D2-309-US (Subjects 30921-0018 and 30937-0129).

Subject 30921-0018, a 53 year old woman assigned to the 0.3 mg CE alone dosage strength (Group F) for 134 days, was diagnosed with adenocarcinoma of the lung following treatment for pneumonia and a persistent cough. She developed severe hypercalcemia, became comatose, and died of cardio-pulmonary failure. The event was considered to be unrelated to study medication by the investigator and medical monitor.
Subject 30937-0129, a 50 year old woman assigned to the 0.45 mg CE/2.5 mg MPA dosage strength (Group D) for 217 days, was diagnosed with lung cancer (type unspecified) and died. The event was considered to be unrelated to study medication by the investigator and medical monitor.

Breast cancer

A total of 8 breast cancers were reported in the sNDA. Seven cases of breast cancers occurred during treatment, and 1 case of breast cancer was reported approximately 1 year after study completion. One case of breast cancer was reported in each of the following four treatment groups: 0.625 mg CE (Group A), 0.625 mg CE/2.5 mg MPA (Group B), 0.45 mg CE/1.5 mg MPA (Group E) and Placebo. Four cases of breast cancer were reported in the 0.3 mg CE/1.5 mg MPA treatment group (Group G). No cases of breast cancer were reported in Group C (0.45 mg CE), Group D (0.45 mg CE/2.5 mg MPA), or Group F (0.3 mg CE) in the sNDA.

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

Two additional cases of breast cancer are reported in the 4-Month Safety Update dated November 30, 2000 (covers the period December 24, 1999 through August 2, 2000). However, when the 4-Month Safety Update was submitted, both cases of breast cancer remain blinded as year 2 of Study 0713D2-309-US was ongoing as of the August 2, 2000 cutoff date of the 4-Month Safety Update. On April 12, 2001, the Sponsor submitted the Second Safety Update, which covers the period August 3, 2000 through April 2, 2001. Because study year 2 of the HOPE study (the substudy) is now completed, the substudy is now unblinded. Subject 30918-0044 was in the placebo treatment group, and Subject 30936-0017 was in the 0.45 mg CE/1.5 mg MPA treatment group.

Three new cases of breast cancer are reported in the Second Safety Update (covers the period August 3, 2000 through April 2, 2001). One case of breast cancer was reported in the 0.45 mg CE alone treatment group (Subject 30919-0112 at cycle 26), and two cases of breast cancer were reported in the 0.3 mg CE alone treatment group (Subject 30936-0033 at approximately 9 months post treatment and Subject 30960-0012 at approximately 42 months post treatment). See Table 7 for the cumulative number of breast cancers reported in the sNDA, 4-Month Safety Update, and the Second Safety Update combined.

Table 7: Breast Cancers Reported in sNDA 4-782/S-115

Treatment by dose (mg) of CE or CE/MPA	Treatment Cycles Completed		
	Cycle 5 to 8	Cycle 12 to 26	Post-Study
Group A 0.625 mg CE	0	Subject 30934-0230, age 51 Screening mammogram = benign appearing calcifications in left breast Cycle 13 mammogram = suspicious appearing microcalcifications of left breast Left breast biopsy = invasive ductal carcinoma, grade I	0
Group B 0.625 mg CE/2.5 mg CE/MPA	Subject 30939-0047, age 60 Screening mammogram = residual scarring; history of left breast atypical lobular hyperplasia Cycle 7 breast biopsy = in situ and invasive moderate to poorly differentiated ductal carcinoma of left breast	0	0
Group C 0.45 mg CE	0	Subject 30919-0112, age 57 Screening mammogram = normal with dense nodular fibroglandular pattern. Cycle 26 left breast biopsy = invasive ductal carcinoma	0
Group D 0.45 mg CE/2.5 mg MPA	0	0	0
Group E 0.45 mg CE/1.5 mg MPA	0	Subject 30936-0017, age 53 Screening mammogram = within normal limits Cycle 26 mammogram = parenchymal distortion Core needle biopsy = invasive ductal carcinoma of the left breast	Subject 30929-0038, age 50 Screening mammogram = left breast cyst Cycle 13 mammogram = isodence right breast mass; ultrasound = simple cysts Ultrasound 1 year post-study = fibroadenoma right breast Excisional biopsy = poorly differentiated infiltrating ductal cell carcinoma
Group F 0.3 mg CE	0	0	Subject 30936-0033, age 50 Screening mammogram = no evidence of malignancy. Cycle 26 mammogram = normal Core needle biopsy of right breast 9 months post-study = infiltrating ductal carcinoma
	0	0	Subject 30960-0012, age 53 Screening mammogram = normal Cycle 13 mammogram = no evidence of malignancy Breast biopsy of right breast 42 months post-study = foci of ductal carcinoma in situ
Group G 0.3 mg CE/1.5 mg MPA	Subject 30946-0088, age 56 Screening mammogram = calcifications in right breast Cycle 8 mammogram = calcifications, parenchymal distortion of right breast Lumpectomy with axillary node dissection = atypical ductal hyperplasia with metastatic carcinoma in 1 of 8 nodes	Subject 30902-0022, age 50 Screening mammogram = normal Cycle 13 mammogram = calcifications in left breast Excisional biopsy = invasive lobular carcinoma of left breast Mastectomy = multi-focal lobular carcinoma; no metastatic foci	0

	0	Subject 30908-0023, age 57 Screening mammogram = negative Cycle 13 mammogram = right breast distortion Core biopsy = invasive ductal adenocarcinoma, grade II	0
	0	Subject 30953-0071, age 58 Screening mammogram = negative Cycle 13 mammogram = left breast mass with spiculated borders Mastectomy = infiltrating ductal carcinoma left breast	0
Group H Placebo	0	Subject 30963-0009, age 59 Screening mammogram = microcalcifications in left breast; screening biopsy = sclerosing adenosis Cycle 13 mammogram = solid mass in right breast Lumpectomy with axillary node dissection = poorly differentiated infiltrating ductal carcinoma; negative nodes	0
	0	Subject 30918-0044, age 52 Screening mammogram = normal Cycle 26 mammogram = abnormal Excisional biopsy = ductal carcinoma in situ, one positive margin	

Source: Adapted from sNDA 4-782, Volume 30, Subsection 10.5.2.1.1, page 176 and the 4-Month and Second Safety Updates.

Per the submission, only two of the above 13 subjects had a history of any prior hormone use. Subject 30902-0022 (Group G) had used oral contraceptives for approximately 6 months in 1972. Subject 30929-0038 (Group E) had used Premarin® and Provera® for approximately 3 months in 1995.

Reviewer's Comments

Thirteen (13) cases of breast cancer were reported in 2,673 treated subjects (11 in active treatment groups, 2 in placebo) over year 1 and year 2 of Study 0713D2-309-US. Three of the 11 cases of breast cancer, in active treatment groups, were diagnosed post-study (range of 9 to 42 months). However, 7 of the 11 cases of breast cancer reported in active treatment groups occurred in CE/MPA combination treatment groups. Only four cases of breast cancer were reported in CE alone groups (1 each in the 0.625 mg CE and 0.45 mg CE treatment groups and two in the 0.3 mg CE treatment group).

Overall, these 13 cases of breast cancer do not represent a higher incidence of breast cancer than reported for other large HRT clinical trials conducted over a two year period.

Arterial thromboses

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

• Subject 30914-0055 was diagnosed with a transient ischemia attack (TIA) during cycle 5 of 0.45 mg CE/1.5 mg MPA treatment (considered to be unrelated to treatment by medical monitor).

• Subject 30931-0045 was diagnosed with a "stroke" during cycle 6 of treatment with 0.625 mg CE (considered to be unrelated to treatment by medical monitor).
• Subject 30940-0041, being treated with 0.625 mg CE/2.5 mg MPA, was diagnosed with a TIA during cycle 5 and discontinued medication on April 25, 1998. On May 21, 1998, she was diagnosed with left parietal subacute cerebral vascular accident (possibly related to study medication per medical monitor).
• Subject 30948-0045 was diagnosed with an acute inferior myocardial infarction during cycle 8 of placebo treatment (considered by medical monitor to be unrelated to study medication). The reviewer acknowledges that a relationship to study medication cannot be ruled out.

No additional cases of arterial thrombosis were reported in the 4-Month Safety Update or the Second Safety Update.

Reviewer's Comments

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

Four reported cases of arterial thrombosis in 2,673 treated subjects do not raise concerns for the reviewer. Other large HRT clinical trials have reported similar or higher numbers of these events. Only one of the four reported cases of arterial thromboses occurred in a CE alone treatment group (1 TIA in the 0.625 mg CE dosage strength).

Venous thromboembolic events

Three (3) venous thromboembolic events are reported in the submission:
• Subject 30953-0031 on 0.45 mg CE/1.5 mg MPA was diagnosed in cycle 9 of treatment with deep vein thrombosis of the left leg (possibly related to study medication per medical monitor).
•Subject 30963-0014 developed a blood clot in cycle 1 of treatment with 0.625 mg CE/2.5 mg MPA after being run over by a car (considered by the investigator to be possibly related to study medication).
•Subject 30965-0050 was diagnosed with a pulmonary embolism during cycle 9 of treatment with 0.45 mg CE (possibly related to study medication per medical monitor).

No additional cases of venous thromboembolic events were reported in the 4-Month Safety Update or the Second Safety Update.

Reviewer's comments

Deep vein thrombosis and pulmonary embolism have been reported in other clinical trials with CE and CE/MPA products approved for HRT. The report of 3 cases of DVT in this clinical trial does not raise concerns for the reviewer.

Cholelithiasis

Five (5) subjects developed cholelithiasis and/or cholecystitis while on study medication during year 1:
1) Subject 30906-0050 during cycle 6 on 0.3 mg CE (possibly drug related);
2) Subject 30911-0040 during cycle 1 on 0.3 mg CE/1.5 mg MPA (possibly drug related);
3) Subject 30922-0006 during cycle 3 on 0.45 mg CE (unrelated per investigator/medical monitor);
4) Subject 30938-0059 during cycle 3 on 0.45 mg CE/2.5 mg MPA (possibly related);
5) Subject 30964-0068 during cycle 3 on 0.45 mg CE/2.5 mg MPA (possibly related).

All five subjects underwent cholecystectomy. Four of the five subjects continued in the study, one subject discontinue from the study prior to her cholecystectomy.

Two additional cases of cholelithiasis were reported in the 4-Month Safety Update. Subject 30918-0026 developed cholelithiasis during cycle 15 and completed the study (cycle 26). The subject had a

cholecystectomy performed post-study. Subject 30965-0042 developed cholelithiasis and pancreatitis during cycle 14. This subject had a laparoscopic cholecystectomy performed and continued the study.

No cases of cholelithiasis were reported in the Second Safety Update.

Reviewer's Comments

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

Endometrium cancer

In year 1 of Study 0713D2-309-US, endometrial biopsies were obtained at cycles 6 and 13. The study procedure for determination of final diagnosis complied with the proposed revised 1995 HRT Guidance, namely: 1) agreement of the two independent, blinded primary pathologists; 2) if disagreement, a third independent, blinded pathologist was consulted; 3) final diagnosis based on the diagnosis of the majority (two out of three). A total of 2,153 subjects were included in the analysis of endometrial hyperplasia or cancer at cycle 13. Five hundred twenty (520) subjects were excluded because no valid endometrial biopsy was obtained during cycles 12 to 14 and no endometrial hyperplasia was diagnosed before cycle 12. One of these subjects did not have a prestudy endometrial biopsy performed.

According to the Sponsor, no endometrial cancer developed during the clinical study. However, two subjects had endometrial biopsy readings of endometrial carcinoma in the 1-year interim analyses submitted. Upon request, the Sponsor provided copies of all pathologists' reports of endometrial biopsy readings for these two subjects (and three additional subjects of interest to the reviewer). These cases are as follows:

• Subject # 30912-0049 in Group E (0.45 mg CE/1.5 mg MPA)

Final prestudy endometrial biopsy diagnosis = Endometrial tissue (other) i.e. benign, inactive or atrophic fragments of endometrial epithelium, glands, stroma, etc.

Cycle 7 endometrial biopsy on 1/12/99

Pathologist 1 = Complex hyperplasia with atypia; hyperplastic focus appears to be in polyp.

Pathologist 2 = Endometrial malignancy; well-differentiated endometrial adenocarcinoma involving endometrial polyp.

Pathologist 3 = Endometrial malignancy; Grade I adenocarcinoma (endometroid/mucinous) in a polyp, mucinous (including intestinal) metaplasia, ciliary change.

Subject withdrawn from the study on 1/25/99

Repeat endometrial biopsy on 1/26/99

Pathologist 1 = Complex hyperplasia with atypia;
a. benign cervical and endometrial fragments
b. complex hyperplasia with atypia, focal

Pathologist 2 = Complex hyperplasia with atypia;
a. focal residual atypical hyperplasia
b. fragments of benign endocervix and endometrium

Total abdominal hysterectomy on [redacted]

Surgical pathology report = Weakly proliferative endometrium, leiomyoma and adenomyosis, no evidence of hyperplasia or carcinoma.

Reviewer's Comments

DRUDP reviewed the pathology reports submitted by the Sponsor. The clinical review team (the reviewer, a second medical officer [also a board-certified pathologist], and the team leader) agree that the final diagnosis for this subject should be well-differentiated endometrial adenocarcinoma, based on the information submitted. In this case, the majority decision (two of the three pathologists) is well-differentiated adenocarcinoma in a polyp, based on the "original" endometrial biopsy slides readings.

• Subject 30924-0011 in Group F (0.3 mg CE)	
Final prestudy endometrial biopsy =	Endometrial tissue (other) i.e. benign, inactive or atrophic fragments of endometrial epithelium, glands, stroma, etc.
Cycle 7 endometrial biopsy on 12/18/97	
Pathologist 1 =	Complex hyperplasia with atypia; prominent eosinophilic metaplasia with surface syncytial changes, recommend full D&C for more complete evaluation of endometrium.
Pathologist 2 =	Endometrial malignancy; FTGO grade 1 adenocarcinoma, focal.
Subject withdrawn from the study on 1/15/98 "Out of study" gynecologic oncologist (not a designated pathology reviewer) review of study endometrial biopsy slides	Severely atypical endometrial hyperplasia.
Repeat endometrial biopsy on 2/13/98 reviewed "out of study"	Scant fragments of surface endometrium with distorted inactive endometrium with focal breakdown and tubal metaplasia.

Reviewer's Comments

Because the third, adjudicating pathologist was not consulted (which is in violation of the protocol-specified procedure), the clinical reviewer followed the most conservative approach and accepted the "worst-case" diagnosis of endometrial adenocarcinoma rendered by pathologist 2. If the most conservative approach were not taken, then the diagnosis by majority decision (2 of 3 pathologists) would be accepted (atypical endometrial hyperplasia). However, this approach would incorporate the diagnosis of an unblinded gynecologic oncologist, outside of the study, which is unacceptable. It should be noted, however, that atypical endometrial hyperplasia is the most pathologically worrisome form of hyperplasia, and is considered to be the true precursor of endometrial cancer.

The three additional requested reports covered Subject # 30908-0003 in the 0.3 mg CE/1.5 mg MPA treatment group and Subjects # 30936-0006 and # 30908-0002 in the 0.625 mg CE alone treatment group. The reviewer concurs with the diagnosis of endometrial hyperplasia in all three cases.

No cases of endometrial cancer occurred during the reporting period covered by the 4-Month Safety Update and the Second Safety Update, December 24, 1999 through April 2, 2001, inclusive.

Reviewer's Comments

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

Endometrial hyperplasia

As reported by the Sponsor in the sNDA, a total of 32 subjects developed hyperplasia by cycle 13 (1.5%, 32 of 2,153 evaluable endometrial biopsies across all 8 treatment groups). However, as previously stated, the clinical review team (the reviewer, a second medical officer {also a board-certified pathologist}, and the team leader) reclassified two cases of reported hyperplasia as endometrial adenocarcinoma (one case each in 0.3 mg CE alone Group E and 0.45 mg CE/1.5 mg MPA Group F). Therefore, a total of 30 subjects developed endometrial hyperplasia and 2 subjects developed endometrial adenocarcinoma in the data submitted to the sNDA.

Twenty-nine (29) of the cases of endometrial hyperplasia reported in the sNDA occurred in the CE alone treatment groups. Only 1 case of endometrial hyperplasia occurred in a CE/MPA treatment group (0.3 mg CE/1.5 mg MPA). In Table 8, the incidence of endometrial hyperplasia alone (not endometrial hyperplasia or cancer) is significantly lower with the corresponding CE/MPA groups (Groups B, D and E) than with the equivalent doses of CE alone (Groups A and C). Zero cases of hyperplasia are reported in Groups B, D and E, in comparison to 20 cases of hyperplasia in Group A (8.03%, 20 of 249 subjects) and 9 cases of hyperplasia in Group C (3.23 %, 9 of 279 subjects). For the 0.3 mg CE/1.5 mg MPA dosage strength (Group G), 1 case of endometrial hyperplasia is reported in comparison to zero cases of endometrial hyperplasia in the equivalent CE alone dose. These results demonstrate a higher endometrial hyperplasia rate for Group G (0.37%, 1 of 272 subjects) over Group F (0.00%). See Table 8.

Table 8: Incidence of Endometrial Hyperplasia at Cycle 13 (1 year), EE Population

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

Source: Adapted from Table 9.2.2.1A, sNDA 4-782, Volume 30, page 95.
[a] Total number of hyperplasias calculated as number of patients.
[b] Confidence intervals calculated by the statistical reviewer.
[c] Individual pairwise comparisons: Groups B with A; D and E with C; G with F, based on Fisher' exact test. Two-sided p-values are shown.

In the submission, rates of endometrial hyperplasia at 1 year were also analyzed by age groups (<50, 50 to 59, and ≥ 60 years of age). However, two reported cases of hyperplasia in the sNDA were reclassified as endometrial adenocarcinoma in this review. Utilizing a combined hyperplasia or cancer rate, subjects who were < 50 years of age had the lowest rate of endometrial hyperplasia regardless of their treatment group (0.45 %, 2 cases of endometrial hyperplasia in 446 subjects < 50). The hyperplasia or cancer rate in subjects 50 to 59 years of age, across all treatment groups, was 1.37% (20 cases of endometrial hyperplasia in 1,454 subjects between ages 59 to 60). Subjects who were ≥ 60 years of age had the highest endometrial hyperplasia or cancer rate (3.56%, 9 cases of endometrial hyperplasia in 253 subjects in the ≥ 60 years age group).

In the 4-Month Safety Update only subjects who reported endometrial hyperplasia as an adverse event were included. As such, this number may not represent all cases of endometrial hyperplasia that occurred during the reporting period. In fact, comparing the data presented, six additional cases of endometrial hyperplasia were identified among the subjects who withdrew from the study for safety-related reasons then were listed under serious adverse events (by comparing subjects numbers). Therefore, at least 14 cases of endometrial hyperplasia occurred between December 23, 1999 and August 2, 2000 (8 cases in the 0.625 mg CE group, 5 cases in the 0.45 mg CE group and 1 case in the 0.3 mg CE group). No cases of endometrial carcinoma were reported.

Three (3) cases of simple hyperplasia without atypia were reported in the Second Safety Update. One case of hyperplasia occurred in the 0.625 mg CE treatment group and two cases of hyperplasia occurred in the 0.45 mg CE alone treatment group. No cases of endometrial carcinoma were reported.

Reviewer's Comments

Overall, the incidence of abnormal endometrial pathology in Study 0713D2-309-US is low. In total, 47 subjects across the 8 treatment groups developed endometrial hyperplasia (2.2%, 47 cases in 2,153 evaluable subjects), and 2 subjects developed endometrial carcinoma. Other large controlled studies of estrogen alone or estrogen/progestin combination HRT drug products have reported endometrial hyperplasia rates ranging from 0% to 40%, and zero to one case of endometrial cancer. The results in Study 0713D2-309-US are consistent with these findings.

The data presented in Table 8 shows a dose-dependent response in endometrial hyperplasia (hyperplasia alone without cancer) within the CE alone groups with the 0.625 mg CE alone treatment group producing the highest endometrial hyperplasia rate and the 0.30 mg CE alone treatment group producing the lowest endometrial hyperplasia rate:

- **hyperplasia rate of 8.03% in Group A (0.625 mg CE)**
- **hyperplasia rate of 3.23% in Group C (0.45 mg CE)**
- **hyperplasia/rate of 0.00% in Group F (0.3 mg CE).**

No cases of hyperplasia were reported in the placebo group.

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

Data presented from the analysis by age groups strengthen the need for prompt endometrial evaluations, when needed to investigate vaginal bleeding in women on HRT therapy, especially for women 60 years of age and older.

Consecutive cycles of amenorrhea

In the HOPE study, bleeding profiles were summarized according to entries recorded by the subject in daily diary cards. Amenorrhea is the desired endpoint for control of bleeding. In the submission, amenorrhea was defined as the absence of any vaginal bleeding or spotting during the 12 study months.

The percentages of subjects in all treatment groups who became amenorrheic and remained so throughout the study year increased with each consecutive cycle. Overall, subjects in the CE-alone and CE/MPA treatment groups exhibited significantly fewer consecutive cycles of amenorrhea than subjects on placebo.

For cycles 1 through 13, all of the CE/MPA combination groups (except Group B) had significantly smaller percentages of subjects exhibiting consecutive cycles of amenorrhea (absence of any bleeding or spotting) versus the corresponding CE alone groups. See representation that follows.

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

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

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

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

Group A	vs. Group B	Group C	vs. Group D -	Group E	Group F	vs. Group G	Group H
0.625	0.625/2.5	0.45	0.45/2.5	0.45/1.5	0.3	0.3/1.5	Placebo
44.0%	62.2%	62.4%	66.2%	62.8%	67.8%	67.6%	69.3%

See Supportive Table 4 in Appendix A of this review for a summary of the number of subjects exhibiting consecutive cycles of amenorrhea for all 8 treatment groups in Study 0713D2-309-US.

Reviewer's Comments

These findings are not unexpected. As the dosage strength of CE alone decreased the percentages of subjects without bleeding or spotting increased. In the active treatment groups (Groups A - G), the percentage of subjects exhibiting cumulative amenorrhea increased with decreasing dosages of CE. The highest CE alone dosage strength (0.625 mg) exhibited fewer cycles without any bleeding or spotting than the 0.45 mg and 0.3 mg dosage strengths. The lowest CE alone dosage strength (0.3 mg) and placebo were not different at any time point analyzed.

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

Treatment Emergent Adverse Events (TEAE)

On June 5, 2001, the Sponsor submitted an amendment to the sNDA with additional database findings that were obtained after the database was locked on December 23, 1999. The new findings submitted are the result of information from clinical research quality assurance reviews, routine data cleanup activities resulting from the quality assurance reviews, and site visits by clinical scientists and associates. As a result of these findings, one additional treatment-emergent adverse event - anxiety - was added to the TEAE table submitted with the proposed labeling. In addition, 14 individual number listings in the TEAE table were corrected. In most cases, one additional number was added. The number and percent was corrected in a few cases. Overall, the new additions do not impact on statistical significance. The reviewer has incorporated these findings in the following table.

Ninety-three percent (93%, n=2,485) of the 2,673 treated subjects in Study 0713D2-309-US reported adverse events. Eighty-nine percent (89%), n = 2,386) of the 2,673 treated subjects in Study 0713D2-309-US reported treatment emergent adverse events (TEAE). Overall, statistically significant differences that are clinically notable include a higher incidence of breast pain in the CE/MPA combination treatment groups than in the CE-alone groups, and the higher incidence of endometrial hyperplasia (previously noted) and vaginal bleeding in

the 0.625 mg CE group (Group A, previously noted). See Table 9 for the number and percent of subjects reporting ≥ 5% treatment emergent adverse events in the 0.45 mg CE and placebo treatment groups. See Supportive Table 5 in Appendix A for the number and percent of subjects reporting ≥ 5% treatment emergent adverse events across all treatment groups in Study 0713D2-309-US.

Table 9: Number (%) of Subjects Reporting ≥ 5% Treatment Emergent Adverse Events Across All Treatment Groups, ITT Population

Body System Adverse event	Group E 0.45 mg CE (n =338)	Group H Placebo (n = 332
Any Adverse Event	305 (90%)	281 (85%)
Body as a Whole		
Abdominal pain	50 (17%)	37 (11%)
Accidental injury	41 (12%)	29 (9%)
Asthenia	23 (7%)	16 (5%)
Back pain	43 (13%)	39 (12%)
Flu syndrome	38 (11%)	35 (11%)
Headache	109 (32%)	93 (28%)
Infection	75 (22%)	74 (22%)
Pain	61 (18%)	61 (18%)
Digestive System		
Constipation	14 (4%)	16 (5%)
Diarrhea	25 (7%)	21 (6%)
Dyspepsia	32 (9%)	46 (14%)
Flatulence	23 (7%)	9 (3%)
Nausea	22 (7%)	31 (9%)
Musculoskeletal System		
Arthralgia	42 (12%)	39 (12%)
Leg cramps	23 (7%)	7 (2%)
Myalgia	18 (5%)	25 (8%)
Nervous System		
Anxiety	12 (4%)	12 (4%)
Depression	27 (8%)	22 (7%)
Dizziness	20 (6%)	17 (5%)
Insomnia	25 (7%)	33 (10%)
Nervousness	17 (5%)	7 (2%)
Respiratory System		
Cough increased	22 (7%)	14 (4%)
Pharyngitis	35 (10%)	38 (11%)
Rhinitis	30 (9%)	42 (13%)
Sinusitis	36 (11%)	24 (7%)
Upper respiratory infection	34 (10%)	35 (11%)
Skin/Appendages		
Pruritis	17 (5%)	7 (2%)
Urogenital System		
Breast enlargement	4 (1%)	3 (<1%)

Breast pain	41 (12%)	29 (9%)
Dysmenorrhea	10 (3%)	2 (<1%)
Leukorrhea	22 (7%)	9 (3%)
Vaginal hemorrhage	14 (4%)	0 (0%)
Vaginal moniliasis	18 (5%)	6 (2%)
Vaginitis	20 (6%)	4 (1%)

Source: Adapted from sNDA 4-782, Volume 30, Table 10.2.2.1A, page 138. Updated per sNDA Amendment dated June 5, 2001.

Reviewer's Comments

Overall, treatment emergent adverse events were similar between the 0.45 mg CE alone and the placebo treatment groups. Headaches were the most frequently reported TEAE for both the 0.45 mg CE and placebo treatment groups (32% and 28%, respectively). Breast pain occurred more frequently in the 0.45 mg CE treatment group than in the placebo group (12% and 9%, respectively). Notably, vaginal hemorrhage (COSTART term that includes vaginal bleeding, intermittent vaginal bleeding, excessive or heavy vaginal bleeding) occurred more frequently in the 0.45 mg CE alone treatment group than in the placebo treatment group (4% compared to 0%, respectively).

Supportive Table 5 in Appendix A of this review shows the number of subjects reporting ≥ 5% treatment emergent adverse events across the 8 treatment groups of Study 0713D2-309-US. The following comments pertain to observations about TEAE across all study groups. Please see Supportive Table 5 in Appendix A of this review.

Although a slightly higher percentages of subjects reported adverse events in the 0.625 mg CE alone group (93%) than in the other treatment groups (range of 87% to 92%), there does not seem to be a strong dose relationship with TEAE overall.

Headaches were the most frequently reported TEAE (29%, range of 26 to 33 % across all treatment groups) followed by infection (20%, range of 18 to 23 %) and breast pain (15%, range of 7 to 26%). Fourteen percent (14%) of the 0.625 mg CE treatment group (47 of 348 subjects) reported vaginal hemorrhage (compared to a range of 2 to 6% in the six other active treatment groups and 0% in the placebo treatment group). This finding clearly demonstrates a dose-dependency.

Of clinical interest, however, is the number of subjects reporting breast pain across all treatment groups. A total of ten percent (10%) of all subjects across the three CE alone treatment groups reported breast pain (103 of 1012 subjects). However, no significant differences are noted between the three CE alone dosage strengths (11% and 12% of the 0.625 mg and 0.45 mg CE groups, respectively and 7% of the 0.3 mg CE alone group). However, twice the number of subjects, 20%, reported breast pain across the four CE/MPA combination treatment groups (264 of 1329 subjects). Adding MPA to CE produced the following comparative breast pain results:

- **0.625 mg CE alone versus 0.625 mg CE/2.5 mg MPA = 11% versus 26%**
- **0.45 mg CE alone versus 0.45 mg CE/2.5 mg MPA = 12% versus 19%**
- **0.45 mg CE alone versus 0.45 mg CE/1.5 mg MPA = 12% versus 21%**
- **0.3 mg CE alone versus 0.3 mg CE/1.3 mg MPA = 7% versus 13 %**

These findings demonstrate a dose-dependent decrease in the percentage of subjects reporting breast pain across the four CE/MPA combination treatment groups.

Also of clinical interest is the difference between the 0.625 mg, 0.45 mg, and 0.3 mg CE groups in reports of vaginal hemorrhage, 14%, 4%, and 2%, respectively. This data also suggest dose-dependency.

Safety-Related Discontinuations

A total of 266 out of 2,673 subjects (10%) discontinued from the study due to an adverse event. Across all 8 treatment groups, discontinuations for any adverse event ranged from 6% for the 0.3 mg CE alone and placebo treatment groups (n=21 for both groups) to 21% for the 0.625 mg CE alone group (n=73). Nine percent of subjects in each of three combination groups (0.625 mg CE/2.5 mg MPA, 0.45 mg CE/1.5 MPA, and 0.3 mg CE/1.5 mg MPA) withdrew for any adverse event (n=31, n=30, and n=30 respectively).

Twelve percent (12%, 43of 348 subjects) of subjects discontinuing in the 0.625 mg CE group reported endometrial hyperplasia and vaginal hemorrhage as the primary reasons for discontinuation. Vaginal hemorrhage alone, as a primary reason for discontinuation, was reported as follows:

CE alone groups:	0.625 mg = 9% (n=32 of 348 subjects)
	0.45 mg = 2% (n=6 of 338 subjects)
	0.3 mg = <1% (n=2 of 326 subjects)
CE/MPA groups:	0.625 mg/2.5 mg = 2% (n=8 of 331 subjects)
	0.45 mg/2.5 mg = 1% (n=4 of 340 subjects)
	0.45 mg/1.5 mg = 2% (n=8 of 331 subjects)
	0.3 mg/1.5 mg = < 1% (n=3 of 327 subjects)

No subjects in the placebo group discontinued because of vaginal hemorrhage or endometrial hyperplasia.

Reviewer's comments

Endometrial hyperplasia and vaginal hemorrhage are clearly associated with discontinuation among subjects assigned to the 0.625 mg CE treatment group.

Metabolic evaluations

A total of 749 of the subjects who were enrolled in Study 0713D2-309-US participated in the metabolic substudy. The metabolic portion of the study included measurements on lipid and glucose/insulin metabolism and coagulation at baseline and cycles 6 and 13.

Lipid metabolism
Mean percent changes from baseline after 6 and 13 cycles are as follows:

Total cholesterol	- In the 0.625 mg and 0.45 mg CE treatment groups, with and without MPA, there was a mean percent decrease in total cholesterol concentrations ranging from 0.22% to 4.58%. - In the 0.3 mg CE alone and with 1.5 mg MPA and placebo groups, there was a mean percent increase ranging from 1.34% to 3.13%.
HDL-cholesterol	- In all treatment groups except placebo, there were statistically significant mean percent increases in HDL-C that ranged from 5% to 18%. - The mean percent increases in HDL-C in the 0.625 mg CE and 0.45 mg CE groups, with and without MPA, and in the 0.3 mg CE alone group were significantly greater than placebo at cycle 13. - The mean percent increase in the 0.3 mg CE/1.5 mg MPA group was not significantly greater than placebo at cycle 13 (p=0.12). - The mean percent increase in HDL-C at cycle 6 in the 0.45mg CE/1.5 mg MPA group was significantly greater than the 0.45 mg CE/2.5 mg MPA group (p=0.009)
HDL_2-cholesterol	- The mean percent increases from baseline HDL_2-C were statistically significant at Cycle 6 in all CE and CE/MPA groups compared with no significant change in the placebo group - The mean percent increases from baseline HDL_2-C were statistically significant at cycle 13 in all CE and CE/MPA groups except for the 0.3 mg CE/1.5 mg MPA group (p=0.72).

LDL-cholesterol	- The mean percent decreases in LDL-C were significantly greater with active treatment than with placebo and were statistically significant within each active treatment group except the 0.3 mg CE/1.5 mg MPA group at cycle 13 (p=0.39). - There was no difference in mean percent decreases in LDL-C in CE and comparable CE/MPA groups. - There was a statistically significant increase in LDL-C (2.95%) in the placebo group at cycle 13.
VLDL-cholesterol	-The mean percent increases in VLDL-C were statistically significant in all treatment groups including placebo. - There were no statistically significant differences between groups.
VLDL-triglycerides	- The mean percent increases in VLDL-TGs after cycles 6 and 13 were statistically significant in all treatment groups except placebo. - There were no statistically significant differences between active treatment and placebo or between CE and corresponding CE/MPA groups.
Triglycerides	- The mean percent increase from baseline TGs at cycles 6 and 13 were statistically significant within in all groups treated with either CE alone or combined with MPA, and after cycle 6 for the placebo group. - The mean percent increase from baseline TGs were statistically significantly greater than placebo after cycles 6 and 13 with the 0.625 mg and 0.45 mg CE groups and the 0.625 mg CE/2.5 mg MPA group; after cycle 6 with the 0.3 mg CE group; and after cycle 13 with the 0.45 mg CE/2.5 mg MPA group. - The mean percent increase from baseline TGs for the 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA groups were not significantly different from placebo at either cycle 6 or cycle 13.

Reviewer's Comments

Overall, these findings show that women treated with CE alone (0.625 mg, 0.45 mg, and 0.3 mg) have a more favorable increase in HDL-C and HDL_2-C concentrations than women treated with CE/MPA. In women treated with CE/MPA, the increase in HDL-C and HDL_2-C concentrations was blunted. The decrease in LDL-C concentrations was similar in women treated with CE alone and CE/MPA.

The 0.625 mg CE group alone or with MPA showed favorable increases in HDL-C and HDL_2-C concentrations and favorable decreases in LDL-C. The 0.45 mg CE group, alone or in combination with MPA, showed similar HDL-C and HDL_2-C results.

Carbohydrate metabolism

The glucose and insulin results from 3-hour GTTs were similar to pretreatment values for all active treatment groups and placebo at cycles 6 and 13. Occasional sporadic mean percent changes from baseline values in the glucose and insulin concentrations were seen at various times during the GTTs. Changes in glucose values were less than 1% of the adjusted mean. The mean percent changes from baseline insulin values were much more variable and ranged from –51 to + 56%. However, there were no statistically significant adjusted mean changes in insulin AUC except for the 0.45 mg CE/2.5 mg MPA dosage strength after cycles 6 and 13 which showed an insulin AUC that was greater than the baseline AUC. Overall, the decreases and increases in glucose and insulin concentrations following glucose challenge did not result in any treatment-related changes in glucose tolerance or the development of insulin resistance.

Coagulation factors

In data submitted, there were some statistically significant increases and decreases from baseline values in clotting times, procoagulant factors, fibrinogen activity, fibrinolytic factors, and anticoagulant factors. However, no consistent changes were noted that would adversely affect hemostasis.

4-Month Safety Update

The 4-Month Safety Update includes data from the year 2 subgroup subjects and covers the period between December 24, 1999 through August 2, 2000. The 4-Month Safety Update includes data on 634 subjects who entered cycle 14. A total of 133 (21%, 133 of 634 subjects) subjects experienced treatment-emergent adverse events. Year 2 of Study 0713D2-309-US was ongoing at the cutoff date of the 4-Month Safety Update. Therefore, treatment group assignments were blinded.

No deaths were reported between December 24, 1999 and August 2, 2000. Thirty-three (33) subjects had one or more adverse events that were considered to be clinically important by the medical monitor. Included among these 33 cases are 8 cases of endometrial hyperplasia; 2 cases of breast cancer; 2 cases of cholelithiasis; 1 case each of lung cancer, thyroid cancer, and bladder cancer; and 1 case of bilateral iliac artery stenosis.

In the 4-Month Safety Update only subjects who reported endometrial hyperplasia as an adverse event were included. As such, this number may not represent all cases of endometrial hyperplasia that occurred during the reporting period. In fact, comparing the data presented, six additional cases of endometrial hyperplasia were identified among the subjects who withdrew from the study for safety-related reasons then were listed under serious adverse events (by comparing subjects numbers). Therefore, at least 14 cases of endometrial hyperplasia occurred between December 23, 1999 and August 2, 2000. No cases of endometrial carcinoma were reported.

Eighty-nine subjects withdrew from the study during this time period. The reason for withdrawal is known for 88 of the 89 subjects (no reason was provided in the case report for one subject). See Table 10.

Table 10: Summary of Subjects Who Withdrew From Year 2 of Study 0713D2-309-US During the Time Period Between December 24, 1999 through August 2, 2000

Reason	Number (%) of Subjects (n = 634)
Any reason	88 (14%)
Adverse event	17 (3%)
Adverse reaction	4 (<1%)
Failed to return	11 (2%)
Other medical event	6 (<1%)
Other nonmedical event	21 (3%)
Subject request	8 (1%)
Protocol violation	13 (2%)
Unsatisfactory response (efficacy)	8 (1%)

Source: 4-Month Safety Update, Volume 1, Table 3, page 10.

Reviewer's Comments

The adverse events reported in the 4-Month Safety Update are not unexpected for a postmenopausal population.

Second Safety Update

The Second Safety Update, submitted on May 15, 2001, covers the period between August 3, 2000 through April 2, 2001. The Second Safety Update includes safety data on 628 subjects whose data were recorded after day 364 of treatment (the substudy) and who were on the database as of August 3, 2000. For this safety update the data are not cumulative. A total of 54 (9% of 628 subjects) subjects experienced treatment emergent adverse events during the period August 3, 2000 through April 2, 2001. Year 2 of the substudy is now completed and unblinded. A final report is in preparation.

No deaths were reported between August 3, 2000 through April 2, 2001. A total of 7 subjects had serious adverse events during this reporting period. Three of the 7 serious adverse events reported in the Second Safety

Update were breast cancers (two diagnosed at the end-of-study and one post-study). The remaining four serious adverse events included one each, multicystic left adnexal mass, left Achilles tendonitis, basal cell carcinoma, and bronchogenic carcinoma.

Of the three new cases of breast cancer reported in the Second Safety Update, one case was reported in the 0.45 mg CE alone treatment group (Subject 30919-0112 at cycle 26), and two cases were reported in the 0.3 mg CE alone treatment group (Subject 30936-0033 at approximately 9 months post treatment and Subject 30960-0012 at approximately 42 months post treatment).

On June 5, 2001, the Sponsor responded to the Division's request for information on the treatment assignment for the two blinded cases of breast cancer reported in the 4-Month Safety Update. Because study year 2 of the HOPE study (the substudy) is now completed, the substudy was unblinded. Subject 30918-0044 was in the placebo treatment group, and Subject 30936-0017 was in the 0.45 mg CE/1.5 mg MPA treatment group.

In addition, on June 5, 2001 the Sponsor provided requested screening mammogram results for the three new cases of breast cancer reported in the Second Safety Update. See Table 7 for the cumulative number of breast cancers reported in the sNDA, 4-Month Safety Update, and the Second Safety Update.

Three (3) cases of simple hyperplasia without atypia were reported in the Second Safety Update. One case of hyperplasia occurred in the 0.625 mg CE treatment group and two cases of hyperplasia occurred in the 0.45 mg CE alone treatment group. No cases of endometrial carcinoma were reported.

Eleven (11) subjects withdrew from the study during this time period. The reason for withdrawal is shown in Table 11.

Table 11: Summary of Subjects Who Withdrew From Study 0713D2-309-US During the Time Period Between August 2, 2000 through April 2, 2001

Reason	Number (%) of Subjects (n = 628)
Any reason	11 (2%)
Adverse event	3 (<1%)
Failed to return	3 (<1%)
Other medical event	3 (<1%)
Other nonmedical event	1 (<1%)
Protocol violation	1 (<1%)

Source: Second Safety Update, Table 3, page 10.

Reviewer's Comments

The adverse events reported in the Second Safety Update are not unexpected for a postmenopausal population between 40 and 65 years of age.

D. Adequacy of safety testing

Prestudy safety assessments were appropriate for the 2-year study. These safety assessments included a complete physical examination including a pelvic examination with a Pap smear, vaginal maturation index, and an endometrial biopsy. A prestudy mammogram was performed unless a written, normal report of a mammogram performed within the pervious 6 months was available (proposed revised 1995 HRT Guidance reduces the acceptable interval to 3 months). A laboratory safety screen was done after a minimum 12-hour fast and included hematologic and blood chemistry tests, urinalysis, and serum FSH and estradiol concentrations were performed. In the substudy group of subjects, additional laboratory assessments were performed including lipid profiles, carbohydrate and coagulation procedures, thyroid stimulating hormone (TSH) and Lp(a) phenotype, and bone markers (serum osteocalcin and urinary calcium, creatinine, and N-telopeptide). In substudy subjects, lipid profiles were assessed twice before treatment, 7 to 14 days apart.

All study subjects were evaluated during cycles 3, 6, 9, and 13. Substudy subjects continuing for year 2 had additional evaluations performed at cycles 16, 19, 22, and 26. The procedures and laboratory tests performed during cycles 3 to 13, and proposed for cycles 16 to 26, are appropriate. Per the study protocol, endometrial biopsies were routinely performed at cycle 6 and 13 during study year 1, and performed during cycle 18 and cycle 26 of study year 2. Endometrial biopsies were obtained during cycle days 15 to 28. Mammograms were repeated at cycle 13 for all study subjects, and were obtained at cycle 26 for substudy subjects.

Reviewer's Comments

These pre-study and on-treatment safety assessments are appropriate for an HRT trial in postmenopausal women.

E. Critical safety findings and limitation of data

In the sNDA submission, the Sponsor reported that no endometrial cancer occurred during the first year of the HOPE study (Study 0713D2-309-US). Proposed labeling reported only the incidence of endometrial hyperplasia in the 1-year interim analysis of the clinical trial data. However, the clinical review team (the reviewer, a second medical officer [also a board-certified pathologist], and the team leader) reviewed copies of all pathologists' reports of endometrial biopsy readings provided by the Sponsor and concluded that two reported hyperplasia readings should be reclassified as endometrial cancer. Please see pages 23-26 of this review for a description of findings and the reviewer's comments.

The WARNING section, [ ] *malignant neoplasms, a. Endometrial cancer* subsection of the proposed labeling has been modified to [ ]

Labeling revisions and status

Recent reviews of several labeling supplements have substantially revised the currently approved labeling for Premarin®. [ ]

In the proposed labeling submitted in the sNDA, six dosage strengths are listed, 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg, and 2.5 mg. Changes have been made to the PHARMACOKINETICS section that include the addition of a Special Population subsection.

A CLINICAL STUDIES section has been added to the proposed label with the following subsections, Information Regarding Effects on Vasomotor Symptoms, Information Regarding Effects on Vulvar and Vaginal Atrophy, Information Regarding Osteoporosis, and Information Regarding Lipid Effects.

The WARNINGS section of the submitted labeling has been changed to incorporate revised language under the *Breast cancer* and *Thromboembolic* [ ] subsections previously provided to the Sponsor in NDA 4-782/Supplements [ ]

The PRECAUTIONS section has been changed to incorporate the *Addition of a progestin when a women has not had a hysterectomy* subsection, and to update the *Cardiovascular* [ ] subsection in accordance with the Division's recommendations previously provided to the Sponsor in NDA 4-782/Supplement [ ] The *Pediatric Use* subsection has been updated, and a *Geriatric Use* subsection has been added.

The Patient Information Insert has been revised in accordance with the plain language initiative.

Reviewer's Comments

The recommended labeling changes will be conveyed to the Sponsor.

VIII. Dosing and administration issues

Premarin® 0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg, and 2.5 mg is approved for continuous oral administration, one tablet daily or cyclic oral administration, one tablet daily for 25 days followed by 5 days pill free. Daily continuous oral administration or cyclic administration of 0.45 mg CE is also recommended.

In the submission, the 0.45 mg CE dosage strength or the 0.625 mg CE dosage strength are recommended as the initial doses for the treatment of moderate-to-severe vasomotor symptoms. Per the Sponsor, the initial starting dose should be dependent on the frequency and severity of symptoms. Attempts to discontinue or adjust medication should be done at 3- to 6-month intervals.

Reviewer's Comments

The DOSING AND ADMINISTRATION section of the proposed labeling has been changed to indicate the following:

[redacted]

IX. Use in special populations

Premarin® is indicated for use in postmenopausal women. Premarin® therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay. The safety and effectiveness of Premarin® in pediatric patients have not otherwise been established.

Subgroups by age were analyzed in the submission. The percentages of women with endometrial hyperplasia increased with age:

- Women < 50 years of age = 0.45% (2 of 446)
- Women 50 to 59 years of age = 1.37% (20 of 1,454)
- Women ≥ 60 years of age = 3.56% (9 of 253)

X. Conclusions and Recommendations

From a clinical perspective, the reviewer recommends approval of the 0.45 mg CE dosage strength. The safety and efficacy data, presented in the sNDA, is adequate to supports the approval of the 0.45 mg CE dosage strength for the treatment of vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause.

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

XI. Appendix A

Appears This Way
On Original

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

Treatment[a] Time Period	Number of Hot Flushes Per Day				
	No. of Patients	Baseline Mean ± SD	Mean Change ± SE	Adjusted Mean ± SE[b]	p-Values v. Placebo[c]
Group A 0.625					
Week 4	27	12.29 ± 3.89	-10.34 ± 0.91	1.96 ± 0.73	<0.001
Week 8	27	12.29 ± 3.89	-11.32 ± 0.94	0.98 ± 0.65	<0.001
Week12	27	12.29 ± 3.89	-11.54 ± 0.89	0.75 ± 0.60	<0.001
Group B 0.635/2.5					
Week 4	34	11.98 ± 3.54	-8.78 ± 0.81	3.38 ± 0.66	<0.001
Week 8	34	11.98 ± 3.54	-10.51 ± 0.84	1.52 ± 0.61	<0.001
Week12	34	11.98 ± 3.54	-10.82 ± 0.79	1.21 ± 0.54	<0.001
Group C 0.45					
Week 4	32	12.25 ± 5.04	-7.21 ± 0.84	5.07 ± 0.67	<0.001
Week 8	32	12.25 ± 5.04	-9.41 ± 0.87	2.84 ± 0.63	<0.001
Week 12	32	12.25 ± 5.04	-9.93 ± 0.82	2.33 ± 0.56	<0.001
Group D 0.45/2.5					
Week 4	28	12.73 ± 3.33	-10.03 ± 0.89	2.57 ± 0.72	<0.001
Week 8	28	12.73 ± 3.33	-11.31 ± 0.93	1.36 ± 0.67	<0.001
Week 12	28	12.73 ± 3.33	-11.51 ± 0.87	1.16 ± 0.59	<0.001
Group E 0.45/1.5					
Week 4	29	12.61 ± 4.29	-8.98 ± 0.88	3.54 ± 0.71	<0.001
Week 8	29	12.61 ± 4.29	-10.39 ± 0.91	2.17 ± 0.66	<0.001
Week 12	29	12.61 ± 4.29	-10.92 ± 0.86	1.64 ± 0.58	<0.001
Group F 0.3					
Week 4	30	13.77 ± 4.78	-9.12 ± 0.86	4.19 ± 0.70	<0.001
Week 8	30	13.77 ± 4.78	-10.76 ± 0.89	2.77 ± 0.65	<0.001
Week 12	30	13.77 ± 4.78	-11.25 ± 0.84	2.29 ± 0.58	<0.001
Group G 0.3/1.5					
Week 4	33	11.30 ± 3.13	-7.60 ± 0.83	4.01 ± 0.67	<0.001
Week 8	33	11.30 ± 3.13	-8.84 ± 0.85	2.63 ± 0.62	<0.001
Week 12	33	11.30 ± 3.13	-10.00 ± 0.80	1.47 ± 0.55	<0.001
Placebo					
Week 4	28	11.69 ± 3.87	-3.80 ± 0.89	8.09 ± 0.72	-
Week 8	28	11.69 ± 3.87	-4.86 ± 0.93	6.93 ± 0.67	-
Week 12	28	11.69 ± 3.87	-5.98 ± 0.87	5.81 ± 0.59	-

Source: NDA 20-527/S-017 Supplement Amendment dated March 15, 2001
[a] Identified by dosage (mg) of CE or CE/MPA.
[b] Standard errors based on assumption of equal variances.
[c] Based on analysis of covariance with treatment as factor and baseline as covariate.

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

Treatment[a] Time Period	Hot Flushes, Mean Severity				
	No. of Patients	Baseline Mean ± SD	Mean Change ± SE	Adjusted Mean ± SE[b]	p-Values v. Placebo[c]
Group A 0.625					
Week 4	27	2.26 ± 0.34	-1.38 ± 0.16	0.90 ± 0.16	<0.001
Week 8	27	2.26 ± 0.34	-1.77 ± 0.16	0.50 ± 0.16	<0.001
Week12	27	2.26 ± 0.34	-1.90 ± 0.17	0.37 ± 0.16	<0.001
Group B 0.635/2.5					
Week 4	34	2.33 ± 0.33	-1.23 ± 0.14	1.07 ± 0.14	<0.001
Week 8	34	2.33 ± 0.33	-1.77 ± 0.15	0.54 ± 0.14	<0.001
Week12	34	2.33 ± 0.33	-1.79 ± 0.15	0.52 ± 0.14	<0.001
Group C 0.45					
Week 4	32	2.23 ± 0.39	0.97 ± 0.14	1.34 ± 0.14	<0.001
Week 8	32	2.23 ± 0.39	-1.33 ± 0.15	0.98 ± 0.15	<0.001
Week 12	32	2.23 ± 0.39	-1.47 ± 0.15	0.85 ± 0.15	<0.001
Group D 0.45/2.5					
Week 4	28	2.29 ± 0.33	-1.30 ± 0.15	0.99 ± 0.15	<0.001
Week 8	28	2.29 ± 0.33	-1.81 ± 0.16	0.48 ± 0.16	<0.001
Week 12	28	2.29 ± 0.33	-1.84 ± 0.16	0.45 ± 0.16	<0.001
Group E 0.45/1.5					
Week 4	29	2.17 ± 0.38	-0.99 ± 0.15	1.27 ± 0.15	<0.001
Week 8	29	2.17 ± 0.38	-1.40 ± 0.16	0.84 ± 0.16	<0.001
Week 12	29	2.17 ± 0.38	-1.54 ± 0.16	0.67 ± 0.16	<0.001
Group F 0.3					
Week 4	30	2.38 ± 0.37	-0.92 ± 0.15	1.40 ± 0.15	<0.001
Week 8	30	2.38 ± 0.37	-1.35 ± 0.16	0.98 ± 0.15	<0.001
Week 12	30	2.38 ± 0.37	-1.27 ± 0.16	1.09 ± 0.15	<0.001
Group G 0.3/1.5					
Week 4	33	2.24 ± 0.31	-0.79 ± 0.14	1.48 ± 0.14	<0.001
Week 8	33	2.24 ± 0.31	-1.34 ± 0.15	0.93 ± 0.15	<0.001
Week 12	33	2.24 ± 0.31	-1.67 ± 0.15	0.58 ± 0.15	<0.001
Placebo					
Week 4	28	2.37 ± 0.34	-0.29 ± 0.15	2.03 ± 0.15	-
Week 8	28	2.37 ± 0.34	-0.57 ± 0.16	1.76 ± 0.16	-
Week 12	28	2.37 ± 0.34	-0.72 ± 0.16	1.62 ± 0.16	-

Source: NDA 20-527/S-017 Supplement Amendment dated March 15, 2001
[a] Identified by dosage (mg) of CE or CE/MPA.
[b] Standard errors based on assumption of equal variances.
[c] Based on analysis of covariance with treatment as factor and baseline as covariate.

Supportive Table 3:
Summary of Maturation Index Results – Mean Values and Comparisons between the Active Treatment Groups and the Placebo Group by Cycle, LOCF

Treatment[a] Time Period	Percentages of Epithelial Cells (%)				
	No. of Patients	Baseline Mean ± SE	Cycle 6 Mean Change ± SE	Cycle 13 Mean Change ± SE	p-Values v. Placebo[b] Cycle 6 - Cycle 13
Group A 0.625					
Superficial	334	6.8 ± 0.6	16.7 ± 1.0	18.2 ± 1.0	<0.001 - <0.001
Intermediate	334	59.3 ± 2.0	6.8 ± 1.9	6.2 ± 2.0	<0.001 - <0.001
Parabasal	334	34.0 ± 2.2	-23.5 ± 2.1	-24.3 ± 2.2	<0.001 - <0.001
Group B 0.635/2.5					
Superficial	318	7.2 ± 0.7	11.9 ± 1.0	12.4 ± 1.0	<0.001 - <0.001
Intermediate	318	55.4 ± 2.0	16.0 ± 2.0	18.4 ± 2.1	<0.001 - <0.001
Parabasal	318	37.5 ± 2.3	-27.9 ± 2.2	-30.9 ± 2.2	<0.001 - <0.001
Group C 0.45					
Superficial	322	7.9 ± 0.8	12.7 ± 1.0	12.9 ± 1.0	<0.001 - <0.001
Intermediate	322	54.7 ± 2.0	14.3 ± 2.0	16.6 ± 2.1	<0.001 - <0.001
Parabasal	322	34.3 ± 2.2	-27.0 ± 2.2	029.5 ± 2.2	<0.001 - <0.001
Group D 0.45/2.5					
Superficial	330	6.1 ± 0.5	11.3 ± 1.0	12.5 ± 1.0	<0.001 - <0.001
Intermediate	330	59.6 ± 2.0	15.5 ± 2.0	16.8 ± 2.0	<0.001 - <0.001
Parabasal	330	34.3 ± 2.2	-26.8 ± 2.1	-29.2 ± 2.2	<0.001 - <0.001
Group E 0.45/1.5					
Superficial	319	6.6 ± 0.7	12.2 ± 1.0	13.5 ± 1.0	<0.001 - <0.001
Intermediate	319	54.3 ± 2.1	18.2 ± 2.0	19.4 ± 2.1	<0.001 - <0.001
Parabasal	319	39.1 ± 2.3	-30.4 ± 2.2	-33.0 ± 2.2	<0.001 - <0.001
Group F 0.3					
Superficial	312	7.9 ± 0.8	10.8 ± 1.1	10.4 ± 1.1	<0.001 - <0.001
Intermediate	312	58.4 ± 2.1	15.1 ± 2.0	17.6 ± 2.1	<0.001 - <0.001
Parabasal	312	33.7 ± 2.3	-25.9 ± 2.2	-28.0 ± 2.3	<0.001 - <0.001
Group G 0.3/1.5					
Superficial	316	7.1 ± 0.7	9.4 ± 1.1	9.7 ± 1.0	<0.001 - <0.001
Intermediate	316	59.6 ± 2.0	17.2 ± 2.0	18.2 ± 2.1	<0.001 - <0.001
Parabasal	316	33.3 ± 2.3	-26.6 ± 2.2	-27.9 ± 2.3	<0.001 - <0.001
Placebo					
Superficial	321	6.8 ± 0.6	0.8 ± 1.0	0.7 ± 1.0	<0.001 - <0.001
Intermediate	321	56.8 ± 2.1	-3.2 ± 2.0	-3.1 ± 2.1	<0.001 - <0.001
Parabasal	321	36.5 ± 2.3	2.4 ± 2.2	2.3 ± 2.2	< 0.001 - <0.001

Source: NDA 20-527/S-017 Supplement Amendment dated March 22, 2001
[a] Identified by dosage (mg) of CE or CE/MPA.
[b] Based on analysis of variance.

Supportive Table 4
Number (%)[a] of Patients Exhibiting Consecutive Cycles of Amenorrhea by Treatment Group[b] – ITT1 Population

Cycles	Group A 0.625 (n = 348)	Group B 0.625/2.5 (n = 331)	Group C 0.45 (n = 338)	Group D 0.45/2.5 (n = 340)	Group E 0.45/1.5 (n = 331)	Group F 0.3 (n = 326)	Group G 0.3/1.5 (n = 327)	Group H Placebo (n = 332)
1 – 13	77 (22.1)	55 (16.6)	130 (38.5)	87 (25.6)	99 (29.9)	143 (43.9)	108 (33.0)	149 (44.9)
2 – 13	82 (23.6)	61 (18 4)	136 (40.2)	97 (28.5)	100 (30.2)	147 (45.1)	116 (35.5)	157 (47.3)
3 – 13	85 (24.4)	69 (20.8)	143 (42.3)	107 (31.5)	104 (31.4)	149 (45.7)	123 (37.6)	160 (48.2)
4 – 13	92 (26.4)	80 (24.2)	150 (44.4)	118 (34.7)	116 (35.0)	152 (46.6)	129 (39.4)	164 (49.4)
5 – 13	96 (27.6)	93 (28.1)	156 (46.2)	123 (36.2)	122 (36.9)	161 (49.4)	138 (42.2)	167 (50.3)
6 – 13	104 (29.9)	98 (29.6)	164 (48.5)	132 (38.8)	128 (38.7)	167 (51.2)	144 (44.0)	169 (50.9)
7 – 13	110 (31.6)	108 (32.6)	171 (50.6)	141 (41.5)	140 (42.3)	173 (53.1)	152 (46.5)	177 (53.3)
8 – 13	113 (32.5)	130 (39.3)	178 (52.7)	157 (46.2)	150 (45.3)	183 (56.1)	165 (50.5)	188 (56.6)
9 – 13	117 (33.6)	143 (43.2)	183 (54.1)	171 (50.3)	161 (48.6)	188 (57.7)	172 (52.6)	195 (58.7)
10 – 13	123 (35.3)	157 (47.4)	190 (56.2)	183 (53.8)	173 (52.3)	195 (59.8)	185 (56.6)	205 (61.7)
11 – 13	130 (37.4)	170 (51.4)	193 (57.1)	197 (57.9)	184 (55.6)	203 (62.3)	198 (60.6)	212 (63.7)
12 – 13	140 (40.2)	187 (56.5)	202 (59.8)	204 (60.0)	198 (59.8)	210 (64.4)	207 (63.3)	221 (66.6)
13 –13	153 (44.0)	206 (62.2)	211 (62.4)	225 (66.2)	208 (62.8)	221 (67.8)	221 67.6)	230 (69.3)

Source: sNDA 4-782/S-115, Volume 42, Supportive Table 91, page 4461.
[a] Percentages were calculated based on the total number of patients enrolled in each treatment group who met the population criteria.
[b] Identified by dosage (mg) of CE or CE/MPA.

Supportive Table 5

Number (%) of Patients Reporting ≥ 5% Treatment Emergent Adverse Events by Treatment Group[a]

Body System Adverse event	Group A 0.635 (n = 348	Group B 0.625/2.5 (n = 331)	Group C 0.45 (n = 338)	Group D 0.45/2.5 (n = 340)	Group E 0.45/1.5 (n = 331)	Group F 0.3 (n = 326)	Group G 0.3/1.5 (n = 327)	Group H Placebo (n = 332)	Total (n = 2673)
Any adverse event	323 (93)	304 (92)	305 (90)	295 (87)	293 (89)	292 (90)	293 (90)	281 (85)	2386 (89)
Body as a Whole									
Abdominal pain	56 (16)	55 (17)	50 (15)	54 (16)	51 (15)	54 (17)	43 (13)	37 (11)	400 (15)
Accidental injury	21 (6)	32 (10)	41 (12)	24 (7)	31 (9)	20 (6)	28 (9)	29 (9)	226 (8)
Asthenia	25 (7)	28 (8)	23 (7)	17 (5)	26 (8)	25 (8)	20 (6)	16 (5)	180 (7)
Back pain	49 (14)	40 (12)	43 (13)	56 (16)	43 (13)	43 (13)	38 (12)	39 (12)	351 (13)
Flu syndrome	38 (11)	27 (8)	38 (11)	42 (12)	36 (11)	34 (10)	34 (10)	35 (11)	284 (11)
Headache	91 (26)	92 (28)	109 (32)	96 (28)	97 (29)	96 (29)	107 (33)	93 (28)	781 (29)
Infection	61 (18)	68 (21)	75 (22)	66 (19)	63 (19)	74 (23)	58 (18)	74 (22)	539 (20)
Pain	58 (17)	45 (14)	61 (18)	54 (16)	48 (15)	66 (20)	64 (20)	61 (18)	457 (17)
Digestive System									
Constipation	16 (5)	12 (4)	14 (4)	21 (6)	16 (5)	16 (5)	14 (4)	16 (5)	125 (5)
Diarrhea	21 (6)	24 (7)	25 (7)	20 (6)	22 (7)	19 (6)	21 (6)	21 (6)	173 (6)
Dyspepsia	33 (9)	28 (8)	32 (9)	37 (11)	27 (8)	36 (11)	27 (8)	46 (14)	266 (10)
Flatulence	24 (7)	22 (7)	23 (7)	26 (8)	27 (8)	18 (6)	15 (5)	9 (3)	164 (6)
Nausea	32 (9)	24 (7)	22 (7)	15 (4)	32 (10)	21 (6)	25 (8)	31 (9)	202 (7)
Musculoskeletal System									
Arthralgia	47 (14)	31 (9)	42 (12)	33 (10)	42 (13)	22 (7)	32 (10)	39 (12)	288 (11)
Leg cramps	10 (5)	23 (7)	23 (7)	21 (6)	17 (5)	11 (3)	13 (4)	7 (2)	134 (5)
Myalgia	18 (5)	15 (5)	18 (5)	16 (5)	18 (5)	29 (9)	14 (4)	25 (8)	153 (6)
Nervous System									
Anxiety	18 (5)	14 (4)	12 (4)	NA	16 (5)	12 (4)	8 (2)	12 (4)	NA
Depression	26 (7)	36 (11)	27 (8)	25 (7)	18 (5)	17 (5)	25 (8)	22 (7)	195 (7)
Dizziness	20 (6)	11 (3)	20 (6)	5 (1)	18 (5)	12 (4)	16 (5)	17 (5)	119 (4)
Insomnia	21 (6)	19 (6)	25 (7)	23 (7)	24 (7)	24 (7)	21 (6)	33 (10)	190 (7)
Nervousness	12 (3)	9 (3)	17 (5)	6 (2)	5 (2)	6 (2)	7 (2)	7 (2)	69 (3)
Respiratory System									
Cough increased	13 (4)	25 (8)	22 (7)	19 (6)	14 (5)	14 (4)	19 (6)	14 (4)	144 (5)

Pharyngitis	35 (10)	38 (11)	35 (10)	36 (11)	28 (8)	40 (12)	29 (9)	38 (11)	279 (10)
Rhinitis	21 (6)	28 (8)	30 (9)	30 (9)	29 (9)	32 (10)	32 (10)	42 (13)	244 (9)
Sinusitis	22 (6)	27 (8)	36 (11)	29 (9)	25 (8)	24 (7)	32 (10)	24 (7)	219 (8)
Upper respiratory infection	42 (12)	34 (10)	34 (10)	38 (11)	31 (9)	28 (9)	36 (11)	35 (11)	278 (10)
Skin and Appendages									
Pruritis	14 (4)	12 (4)	17 (5)	10 (3)	15 (5)	16 (5)	16 (5)	7 (2)	107 (4)
Urogenital System									
Breast enlargement	3 (<1)	18 (5)	4 (1)	10 (3)	9 (3)	7 (2)	5 (2)	3 (<1)	59 (2)
Breast pain	39 (11)	87 (26)	42 (12)	64 (19)	71 (21)	24 (7)	42 (13)	29 (9)	396 (15)
Dysmenorrhea	13 (4)	15 (5)	10 (3)	9 (3)	19 (6)	4 (1)	10 (3)	2(<1)	82 (3)
Leukorrhea	18 (5)	12 (4)	22 (7)	17 (5)	15 (5)	13 (4)	10 (3)	9 (3)	116 (4)
Vaginal hemorrhage	47 (14)	19 (6)	14 (4)	12 (4)	14 (4)	7 (2)	8 (2)	0	121 (4)
Vaginal moniliasis	20 (6)	27 (8)	18 (5)	18 (5)	24 (7)	17 (5)	14 (4)	6 (2)	144 (5)
Vaginitis	24 (7)	18 (5)	20 (6)	14 (4)	19 (6)	16 (5)	14 (4)	4 (1)	129 (5)

Source: sNDA 4-782/S-115, Volume 30, Table 10.2.2.1A, page 138 and amendment submitted to sNDA dated June 5,2001.
NA = Not available
[a] Identified by dosage (mg) of CE or CE/MPA.

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/s/

Theresa Van Der Vlugt
7/31/01 11:44:07 AM
MEDICAL OFFICER
Primary review of supplemental NDA for 0.45 mg conjugated estrogens

Shelley Slaughter
7/31/01 12:01:17 PM
MEDICAL OFFICER
I concur.

Medical Officer's Review

NDA 4-782/S-115 and SLR-130
Labeling Review

Date S-115 Submitted:	**10/28/02**
Date SLR-130 Submitted:	**2/11/03**
Review Finalized:	**4/24/03**

Sponsor:	**Wyeth Pharmaceuticals** **P.O. Box 8299** **Philadelphia, PA 19101-8299**
Drug Name:	
Generic:	**Conjugated Estrogens (CE)**
Trade:	**Premarin®**
Pharmacologic category:	**Estrogen**
Route of Administration:	**Oral**
Dosage Form:	**Tablet**
Strength:	**0.45 mg CE**
Proposed Indications:	**1) Treatment of moderate to severe vasomotor symptoms associated with the menopause.** **2) Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.**
Related Submissions:	**NDA 20-527** **IND 21,696**

Background

Premarin® (1.25 mg conjugated estrogens) was approved in 1942 for the relief of vasomotor symptoms. In 1972, the Federal Register Drug Efficacy Study Implementation Notice (DESI 1543:37 FR 14826 dated July 25, 1972), which was based on the National Academy of Sciences-National Research Council Drug Efficacy Study Group (NAS-NRC) review of published literature, found non-contraceptive estrogen drugs (including Premarin®) effective for several "DESI Indications". This 1972 notice and two additional notices (DESI 1543: 41 FR 43114 dated September 29, 1976 and 51 FR 12568 dated April 11, 1986) defined these "DESI Indications" as follows: moderate to severe vasomotor symptoms (MSVS) associated with the menopause, senile vaginitis, kraurosis vulvae, pruritis vulvae, abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, female hypogonadism, amenorrhea, female castration, primary ovarian failure, prevention of postpartum breast engorgement, palliation of selected cases of inoperable progressing mammary and prostatic carcinoma, and postmenopausal osteoporosis.

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

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

Five dosage strengths of Premarin® are currently approved, 0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg, and 2.5 mg. Premarin® is administered orally in a continuous daily regimen or in cyclical regimens (regimens such as 25 days on drug followed by five days off drug) as is medically appropriate on an individualized patient basis.

Premarin® therapy is indicated in the:

1. Treatment of moderate to severe vasomotor symptoms (VMS) associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
4. Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
5. Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).
6. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

On December 30, 1994, with the initial approval of PREMPRO™ and PREMPHASE®, the Agency requested a Phase 4 commitment to investigate the lowest dose combinations of CE/MPA for the prevention of postmenopausal osteoporosis. Study 0713D2-309-US, submitted to NDA 4-782/S-115 on July 31, 2000, included 8 treatment groups:

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

On July 31, 2001, Premarin 0.45 mg received an approvable action from the Agency for the treatment of moderate to severe vasomotor symptoms associated with the menopause and moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. The sponsor was advised that before the application could be approved it would be necessary to address the following:

- A number of deficiencies noted during inspection of the Guayama, Puerto Rico manufacturing facility;
- A number of deficiencies noted during inspection of the Rouses Point, New York manufacturing facility; and
- Submit copies of final printed labeling revised as the enclosed labeling for NDA 4-782/S-115.

In a letter dated October 28, 2002, the Sponsor provided a complete response to the approvable letter of July 31, 2001, stating the following:

1. "**Manufacturing facility** – With regard to the Guayama, Puerto Rico and Rouses Point, New York manufacturing facilities and references in the approvable letter to the deficiencies noted by the inspector, inspections were conducted by the Agency utilizing Compliance Program Guidance Manual Program 7356.002, which establishes a systems approach to inspection coverage, in February/March 2002 (Guayama) and April/May 2002 (Rouses Point). Both facilities were found to be operating in compliance with cGMPs."
2. **"Labeling** – The enclosed proposed labeling for Premarin 0.45 mg has taken into account the Division's comments provided in the July 31, 2001 approvable letter as well as includes the proposed language to address the Women's Health Initiative (WHI) results (*Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women, JAMA, July 17, 2002, Vol. 288, No. 3*) and the National Cancer Institute cohort study concerning ovarian cancer (*Menopausal Hormone Replacement Therapy and Risk of Ovarian Cancer, JAMA, July 17, 2002, Vol. 288, No.*

3) submitted in the "changes being effected" supplement for Premarin tablets, NDA 4-782, on August 23, 2002."

3. The storage statement on the container and carton labels has been revised to "Store at 20-25°C ([ ]°F). [See USP Controlled Room Temperature]"
4. **Safety Profile** – To satisfy this request, reference is made to NDA 21-417, submitted to the Division of Metabolic and Endocrine Drug Products on December 17, 2001, and the subsequent 4-month safety update submitted to DMEDP on April 17, 2002. NDA 21-417 provided safety data from Years 1 and 2 of the HOPE Study (Protocol 0713D2-309-US)."

On February 11, 2003, the Sponsor submitted a Special Supplement – Changes Being Effected (SLR-130, CBE 0) to provide for minor revisions in the text of the **CLINICAL PHARMACOLOGY** section and add safety information to the **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS** sections of labeling. Minor revisions to the test of the **PATIENT INFORMATION** leaflet were also submitted.

On February 28, 2003, the Office of Compliance advised the Division of Reproductive and Urologic Drug Products (DRUDP) that the Establishment Evaluation System (EES) had been updated to reflect an acceptable GMP status for NDA 4-782/S-115 for 0.45 mg Premarin®.

Chemistry, Manufacturing and Controls

Please see the Chemistry, Manufacturing and Controls Review.

Final Labeling

The proposed labeling submitted was modified in accordance with the Agency's 2003 draft labeling guidance entitled, "Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Prescribing Information for Health Care Providers and Patient Labeling" (see **Federal Register**/ Volume 68/ Monday, February 3, 2003/Notices), and the Premarin® approved labeling dated January 3, 2003.

The **BOXED WARNING** was expanded to include information regarding **CARDIOVASCULAR AND OTHER RISKS**. Minor revisions have been made to the **CLINICAL PHARMACOLOGY** section under the **Pharmacokinetics** subsections to update the text and Table 1.

Minor revisions have been made to the **Clinical Studies** subsections to update Table 2 under ***Effects on vasomotor symptoms***.

A ***Women's Health Initiative Studies*** subsection (text and Table 7) has been added.

Per the draft labeling guidance for noncontraceptive estrogen drug products and NDA 4-782/SLR-130, the following sections have been revised accordingly: **INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS,** and **DOSAGE AND ADMINISTRATION**.

The **PATIENT INFORMATION** insert has been modified in compliance with the plain language initiative, recommendations from the Division of Drug Marketing, Advertising and Communications (DDMAC) and the Division of Surveillance, Research & Communication Support (DSRCS), the Agency's 2003 draft labeling guidance for noncontraceptive estrogen drug products and NDA 4-782/SLR-130.

Please see the attached Premarin® label.

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
4/24/03 02:07:52 PM
MEDICAL OFFICER

Shelley Slaughter
4/24/03 02:15:44 PM
MEDICAL OFFICER
I concur with this labeling review.

Premarin™ Team Leader Review

NDA:	**4-782, S-115**
Drug:	**Premarin®**
Proposed Indications:	**1. Treatment of moderate-to-severe vasomotor symptoms** **2. Treatment of vulvar and vaginal atrophy**
Dosage/Form/Route:	**0.45 mg conjugated estrogens**
Applicant:	**Wyeth-Ayerst Research**
Original Submission Date:	**July 31, 2000**
Primary Review Finalized:	**July 18, 2001**
Date of Memorandum:	**July 23, 2001**

Background and Regulatory History

Premarin ® (1.25 mg conjugated estrogens) was approved in 1942 for the relief of vasomotor symptoms. In 1972, the Federal Register Drug Efficacy Study Implementation Notice (DESI 1533.37 FR 14826 dated July 31, 1972) which was based on the National Academy of Sciences-National Research Council Drug Efficacy Study Group (NAS-NRC) review of published literature, found non-contraceptive estrogen drugs (including Premarin®) to be effective for several "DESI Indications". This 1972 notice and two additional notices (DESI 1543, 41 FR$#114 dated September 29, 1976 and 51 FR 12568 dated April 11, 1986) defined these "DESI Indications" as follows:

1. moderate-to-severe vasomotor symptoms (MSVS) associated with the menopause;
2. senile vaginitis;
3. kraurosis vulvae;
4. pruritis vulvae;
5. abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology;
6. female hypogonadism;
7. amenorrhea;
8. female castration;

9. primary ovarian failure;

10. prevention of postpartum breast engorgement;

11. palliation of selected cases of inoperable progressing mammary and prostatic carcinoma; and

12. postmenopausal osteoporosis.

On September 29, 1976, Federal Register notice 41 FR 43108 instituted "class labeling" for estrogen products. The purpose was to introduce uniform labeling with respect to benefits and risks of these products.

Wyeth-Ayerst received approval for NDA 20-303 on December 30, 1994 to market Prempro™ and Premphase®, two oral combination drug products consisting of conjugated estrogens (CE) and medroxyprogesterone acetate (MPA). One dosage strength of Prempro™, Prempro™2.5 (0.625 mg CE/2.5 mg MPA), and Premphase® were approved. Initially, Prempro™2.5 and Premphase® were co-packaged products. Prempro™ consisted of one tablet of CE and one tablet of MPA taken on a continuous daily basis and Premphase® consisted of one tablet of CE taken on days 1-14 of the month and one tablet of CE and one tablet of MPA taken on days 15-28 of the month. On November 17, 1995, the Agency approved NDA 20-527 for Prempro™ 2.5, a single tablet of 0.625 mg CE/2.5 mg MPA taken on a continuous daily basis and Premphase®, a single tablet of 0.625 mg CE taken for days 1-14 of the month and a single tablet of 0.625 mg CE/5 mg MPA taken for days 15-28 of the month. NDA 20-527, Supplement 006 for Prempro™ 5 (0.625 mg CE/5 mg MPA in a single tablet taken on a continuous daily basis) was approved on January 9, 1998. Prempro™ 2.5, Prempro™ 5, and Premphase® are all approved for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause (VMS) in women with a uterus, treatment of vulvar and vaginal atrophy associated with the menopause (VVA) in women with a uterus, and prevention of osteoporosis.

With the initial approval of Prempro™ and Premphase®, the Agency requested from Wyeth-Ayerst a Phase 4 commitment to investigate the lowest dose combination of CE and MPA for the prevention of osteoporosis. Study 0713D2-309-US originally was designed to investigate the lowest combination conjugated estrogen (CE)/medroxyprogesterone acetate (MPA) dose for the prevention of postmenopausal osteoporosis. It was a controlled 24-month Phase 3 clinical trial with three CE alone arms (0.3 mg, 0.45 mg and 0.625 mg), four combination CE/MPA arms and one placebo arm. The unblinding strategy to assemble and analyze the interim year 1 data for Study 0713D2-309-US while preserving the integrity of the ongoing study was presented to the Agency on December 9, 1999. The Agency concurred with the proposed unblinding procedures on December 16, 1999.

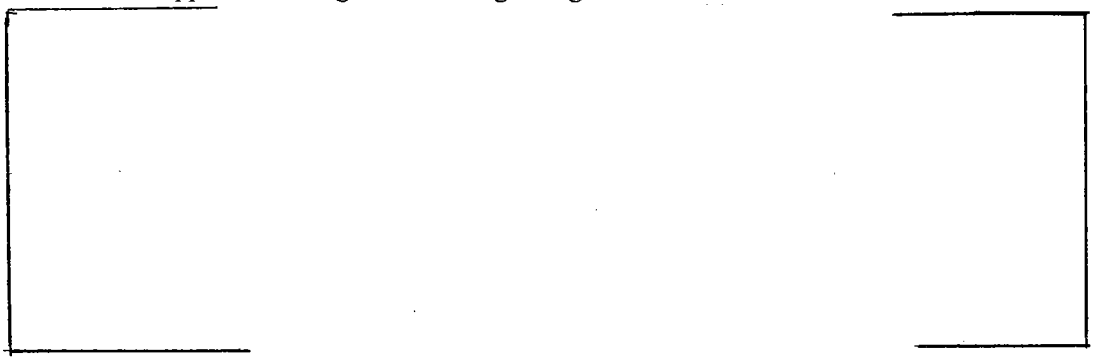
On July 31, 2000 Wyeth-Ayerst submitted NDA 4-782, Supplement 115 (S-115) that presented the year 1 interim analyses of efficacy and safety data from Study 0713D2-309-US to support the approval of the 0.45 mg CE dosage strength for VMS and VVA. No data is presented regarding the prevention of osteoporosis. Year 2 of Study 0713D2-309-US was ongoing at the time of submission of S-115. S-115 was filed on October 1, 2000.

Chemistry, Manufacturing, and Controls (CMC)

The following summary addresses the major issues identified in the chemistry review.

The drug substance is conjugated estrogens and the drug substance is unchanged from what is described in NDA 4-782 (conjugated estrogens tablets). The certificate of analysis for the batch used in the drug product stability studies has been provided and conforms to the drug substance regulatory specifications.

The formulation and manufacturing procedure of the drug product (0.45 mg strength tablet) is based on the approved 0.3 mg and 0.625 mg strength tablets. [



]

An establishment evaluation request (EER) was submitted on September 19, 2000 and an overall recommendation from the Office of Compliance is pending. One site for conjugated estrogens drug substance manufacturing (Ayerst Organics, Inc. in Manitoba Canada) was returned as acceptable based on an October 31, 2000 inspection. The other site for CE drug substance manufacturing (Wyeth Laboratories in Rouses Point, NY) was issued a withhold recommendation by the District, with a pending regulatory action. The two sites for drug product co-manufacturing, Wyeth Laboratories in Rouses Point, NY and Wyeth Ayerst Pharmaceuticals in Guayama, Puerto Rico were also issued a withhold recommendation by the District, with a pending regulatory action.

From a Chemistry, Manufacturing and Controls point of view the NDA is approvable. The NDA may be approved pending an acceptable cGMP status of the manufacturing facilities and satisfactory resolution of the CMC labeling issues.

Preclinical Pharmacology and Toxicology

The Preclinical Pharmacology review notes that Premarin® is an approved drug and S-115 is for a lower dose. There are no safety concerns from a pharmacology/toxicology standpoint and no pharmacology review is necessary.

Clinical Pharmacology and Biopharmaceutics

The Sponsor conducted a relative bioavailability study, Study 0713D2-119-US, to support the Human Pharmacokinetics and Bioavailability section of S-115. This study was a randomized, single dose, 4-period/treatment crossover study that evaluated the following estrogen/progestin combination or estrogen-alone doses: 2 x 0.625 mg CE/2.5 mg MPA, 2 x 0.45 mg CE/ 2.5 mg MPA, 2 x 0.45 mg CE/1.5 mg MPA, and 2 x 0.45 mg CE. The following conclusions were made based on the Biopharmaceutics review of Study 0713D2-119-US and other information submitted to S-115. The PK of CE upon administration of the 0.45 mg CE tablet is comparable to the PK of CE upon administration of 0.45 mg CE/1.5 mg MPA tablets. However, the unconjugated 17β-estradiol t_{max} was 17.5 ± 9.8 hours for the 0.45 mg CE tablet and 14.5 ± 7.3 hours for the 0.45 mg

CE/1.5 mg MPA tablet. The single dose bioavailability study does not address the dose accumulation potential upon multiple-dose administration. No multiple dose CE PK information is in the current Premarin® labeling. Lack of multiple dose PK information for the 0.45 mg CE oral tablet may not be a critical issue for this efficacy supplement. The CE present in the 0.45 mg CE tablets is identical to that in the marketed Premarin® products. The 0.45 mg CE tablet uses the same formulation technology as the marketed Premarin® products. The CE formulation tested in the clinical studies , Study 0713D2-309-US and Study 0713D2-119-US is identical to the to-be-marketed formulations in terms of scale of manufacture and composition except the color coat, which is white in the clinical formulation. The color change between the clinical batch and the to-be-marketed batch was justified by *in vitro* dissolution data. Based on the individual dissolution profiles and the f_2 values, the clinically-tested 0.45 mg CE tablets and the to-be-marketed 0.45 mg CE tablets are deemed to be similar.

The Sponsor's proposed in vitro dissolution method and specifications for the 0.45 mg CE tablet are acceptable.

The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation II (OCPB DPEII) finds the information submitted in the NDA to be acceptable.

Division of Scientific Investigations (DSI) Report

Following the DSI guidelines regarding criteria for requesting inspection of clinical sites, the medical officer determined that this efficacy supplement had no specific safety concerns and did not require inspection.

Clinical

Study 0713D2-309-US, the Health and Osteoporosis, Progestin and Estrogen Study (HOPE) study was a 2 year prospective, multi-center, double-blind, randomized, parallel-group, active- and placebo-controlled Phase 3 study. Each study subject took both an active drug and placebo control tablet except those subjects randomized to the placebo group who took two placebo tablets. Subjects were encouraged to take study medication at approximately the same time each day. In addition to the study medication, all study subjects received 1 tablet of Caltrate®, 600 mg elemental calcium. Two thousand eight hundred five (2,805) subjects were randomized into 8 treatment groups. Of these 2,805 subjects randomized, 132 subjects do not appear in the analyses. Eighty one (81) subjects provided no medication use data and 51 subjects were excluded by the Sponsor (the clinical review team concurs) from the efficacy analyses because they participated at a Clinical Site (30952) that was terminated because of noncompliance with Good Clinical Practice. Two thousand six hundred seventy three (2,673) women took medication and were included in the efficacy analysis (the basic study group). The numbers of subjects per treatment group included in the efficacy analyses are as follows:

Group A: 0.625 mg CE – 348 subjects
Group B: 0.625 mg CE/2.5 mg MPA – 331 subjects
Group C: 0.45 mg CE – 338 subjects
Group D: 0.45 mg CE/2.5 mg MPA – 340 subjects
Group E: 0.45 mg CE/1.5 mg MPA – 331 subjects
Group F: 0.3 mg CE – 326 subjects
Group G 0.3 mg CE/1.5 mg MPA – 327 subjects
Group H: placebo- 332 subjects

As indicated above, the Agency agreed with the plan to perform interim analyses of the data for VMS, VVA and protection of the endometrium. Only 9% (241) of the 2,673 treated subjects met the 1995 Guidance for Clinical Evaluation Of Combination Estrogen/Progestin-Containing Drug Products Used For Hormone Replacement Therapy of Postmenopausal Women (HRT Guidance)–specified number of moderate-to-severe vasomotor symptoms (7-8 per day or 50-60 per week) to be enrolled in a study to assess VMS. The Sponsor's original efficacy analysis for VMS utilized a baseline adjusted mean value and did not include last observation carried forward (LOCF). For consistency (with regard to the approved Label), the Sponsor was asked to provide efficacy analysis with the mean change and not baseline adjusted mean and to impute missing data with a LOCF approach. The efficacy analyses for those subjects meeting the requisite number of moderate-to-severe vasomotor symptoms (MSVS) are presented in Tables 1 and 2 which are modified from the medical officer's (MO) Tables 2 and 3.

Table 1: Mean Daily Number of Moderate-to-Severe Hot Flushes and Change from Baseline in Mean Daily Number of Moderate-to-Severe Hot Flushes during Therapy in All Subjects with Moderate-to-Severe Hot Flushes Per Day at Baseline, Intent-to-Treat Population with LOCF[a]

Week	0.45 mg CE n=32	Placebo n=28
Baseline		
Mean Number	12.25	11.69
Week 4		
Mean Number	5.07	8.09
Mean Change[b]	-7.21	-3.80
p-value vs. placebo[c]	<0.001	N/A
Week 8		
Mean Number	2.84	6.93
Mean Change[b]	-9.41	-4.86
p-value vs. placebo[c]	<0.001	N/A
Week 12		
Mean Number	2.33	5.81
Mean Change[b]	-9.93	-5.98
p-value vs. placebo[c]	<0.001	N/A

[a]LOCF = last observation carried forward
[b]Mean change from baseline
[c]p-value is based on analysis of covariance with treatment as factor and baseline as covariate

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Table 2. Mean Daily Severity and Change from Baseline in the Mean Daily Severity of Hot Flushes during Therapy in All Subjects with Moderate-to-Severe Hot Flushes Per Day at Baseline, Intent-to-Treat Population with LOCF[a]

Week	0.45 mg CE n=32	Placebo n=28
Baseline		
Mean Severity	2.23	2.37
Week 4		
Mean Severity	1.34	2.03
Mean Change[b]	-0.97	-0.29
p-value vs. placebo[c]	<0.001	N/A
Week 8		
Mean Severity	0.98	1.76
Mean Change[b]	-1.33	-0.57
p-value vs. placebo[c]	<0.001	N/A
Week 12		
Mean Severity	0.85	1.62
Mean Change[b]	-1.47	-0.72
p-value vs. placebo[c]	<0.001	N/A

[a]LOCF = last observation carried forward
[b]Mean change from baseline
[c]p-value is based on analysis of covariance with treatment as factor and baseline as covariate

The 0.45 mg CE showed a statistically significant reduction in MSVS (frequency and severity) when compared to placebo at Week 4 and Week 12. There is a decrease of greater than 2 moderate-to-severe hot flushes per day in the 0.45 mg CE compared to the placebo that is apparent at Week 4 and maintained through Week 12. In addition, the Sponsor also performed subgroup analysis of VMS by age in those subjects who completed 12 weeks of treatment. This analysis was not performed on the ITT population used by the clinical review team to establish efficacy. The results by age group (<50, 50-59, ≥ 60) of the subgroup analysis showed that in women < 50, there was a delay in treatment effect for frequency (p=0.053 at week 4 and p=0.014 at week 8) and a non-sustained treatment effect for severity (statistically significant reduction at week 4 and 8, but p=0.67 at week 12) for the 0.45 CE group. In women aged 50-59, the 0.45 mg CE demonstrated showed a consistent statistically significant reduction in frequency of hot flushes at all time points, however, the reduction in severity was not sustained from week 8 to 12 (p=0.11 at week 12). The number of women in the age range ≥ 60 was too small to permit an observational assessment of treatment effect.

The efficacy in treatment of VVA was assessed utilizing baseline, on-treatment and end-of-study vaginal cytology smears to determine the maturation index (MI= the percentage of parabasal, intermediate and superficial cells). The Division now strongly recommends that studies for efficacy in the treatment of VVA assess physician-determined signs and patient's symptoms in addition to the MI. However, this recommendation was not being made when the original protocol for the HOPE study was reviewed. MI data is presented in Table 3 that was modified from the MO's Table 4.

Table 3. Maturation Index per Treatment Group assessed between Cycles 5-7 and Cycles 12-14, ITT Population

Treatment	Baseline Mean ±SE	Cycle 6 Mean Change± SE	Cycle 13 Mean Change ±SE
0.45 mg CE			
Parabasal Cells (%)	34.3 ±2.2	-27.0 ± 2.2	-29.5 ± 2.2
Intermediate Cells (%)	54.7 ± 2.0	14.3 ± 2.0	16.6 ± 2.1
Superficial Cells (%)	7.9 ± 0.8	12.7 ± 1.0	12.9 ± 2.2
p-value vs. placebo		≤0.001	≤0.001
Placebo			
Parabasal Cells (%)	36.5 ± 2.3	2.4 ± 2.2	2.3 ± 2.2
Intermediate Cells (%)	56.8±2.1	-3.2 ± 2.0	-3.1±2.1
Superficial Cells (%)	6.8 ± 0.6	0.8 ± 1.0	0.7 ± 1.0

Table 3 demonstrates that an estrogenic effect is shown at both cycle 6 and cycle 13 for 0.45 mg CE dosage strength.

Two deaths were reported during Study 0713D2-309-US. Both of these were lung cancer deaths and were considered unrelated to study drug medication. Eight breast cancers were reported in the interim analysis at 1 year of study 0713D2-309-US. Seven of these cancers occurred during treatment and 1 case was diagnosed 1 year after treatment and is reported in the interim analysis. Four of the breast cancers were in the 0.3mg CE/1.5 mg MPA treatment group and 1 case of breast cancer was reported in each of the 0.625 mg CE, the 0.625mg CE/2.5 mg MPA, the 0.45 mg CE/1.5 mg MPA and placebo treatment groups. No cases of breast cancer were seen in the 0.45 mg CE, the 0.45mg CE/2.5 mg MPA or the 0.3 mg CE treatment groups. In addition to the 8 cases of breast cancer, one subject (# 30919-0066 randomized to Placebo) had a mammogram-directed biopsy consistent with lobular carcinoma in situ, multiple foci, with calcifications, cystic change, and apocrine metaplasia. This lesion is considered pre-cancerous. Two additional cases of breast cancer (in Subject 30918-0044 and Subject 30936-0017) were reported in the 4-month update of safety, but were blinded as to treatment group at the time of the cut-off date (August 2, 2000) for that safety update. On April 12, 2001, the Sponsor submitted the Second Safety Update, which covers the period August 3, 2000 through April 2, 2001. The sub-study data was unblinded at that point and it is known that Subject 30918-0044 was on placebo and Subject 30936-0017 was in the 0.45 mg CE/1.5 mg MPA treatment. Three new cases of breast cancer were reported in the Second Safety Update. One case was reported in the 0.45 mg CE alone group (Subject 30919-0112 at cycle 26) and two cases in the 0.3 mg CE alone treatment group (Subject 30936-0033 at approximately 9 months post treatment and Subject 30960-0012 at approximately 42 months post treatment). Overall, 13 cases of breast cancer were reported in 2,673 treated subjects (11 in active treatment groups and 2 in placebo) over years 1 and 2 of Study 0713D2-309-US. Three of the 11 cases of breast cancer (all in active treatment groups) were diagnosed post-study (range of 9 to 42 months). Seven of the 11 cases of breast cancer in active treatment groups occurred in subjects on CE/MPA combinations. In the CE alone treatment groups, 1 case each of breast cancer were reported in 0.4mg CE and the 0.625 mg CE treatment groups while two cases were reported in the 0.3 mg CE treatment group. Thirteen cases of breast cancer in 2,673 treated subjects do not represent a higher incidence of breast cancer in this trial than the reported incidence with other large HRT studies conducted over a two year period.

There were 4 cases of arterial thrombosis reported in Study 0713D2-309-US. These cases included: 1 case of transient ischemic attack (TIA) during cycle 5 in a subject on 0.45 mg CE/1.5

mg MPA; 1 subject on 0.625 mg CE/2.5 mg MPA with a TIA at cycle 5 who approximately 1 month later was reported to have a left parietal subacute cerebral vascular accident; 1 case of stroke during cycle 6 in a subject on 0.625 mg CE; and 1 case of myocardial infarction at cycle 8 in a subject on placebo. No cases of arterial thromboses were reported in the 0.45 mg CE treatment group and no additional cases of arterial thrombosis were reported in the 4-Month Safety Update or the Second Safety Update.

Three venous thromboembolic events were reported in Study 0713D2-309-US. These include a pulmonary embolus diagnosed at cycle 9 in a subject in the 0.45 mg CE group. This was categorized as possibly related to study drug by the medical monitor for the trial. The other cases of venous thromboembolic events occurred in combination CE/MPA groups. They included a DVT diagnosed at cycle 9 in a subject treated with 0.45 mg CE/1.5 mg MPA and a blood clot diagnosed at cycle 1 in a subject (treated with 0.625mg CE/2.5 mg MPA) following an automobile accident. Three cases of venous thromboembolic events in 2, 673 subjects do not raise a safety concern regarding the approval of the 0.45 mg Premarin® dose.

Five cases of cholelithiasis or cholecystitis occurred in subjects while on study medication in year 1 of Study 0713D2-309-US. These 5 subjects underwent cholecystectomy and four of the five continued in the study. One of the cases was in subjects treated with 0.45 mg CE. Two additional cases of cholelithiasis were reported in the 4-Month Safety Update. One subject developed cholelithiasis at cycle 15 and completed the study and received a cholecystectomy post-study. A second subject developed cholelithiasis and pancreatitis at cycle 14. She had a laparoscopic cholecystectomy and continued the study. No additional cases of cholelitiasis were reported with the Second Safety Update. No safety concerns regarding the risk of cholelithiasis with 0.45 mg CE are raised with this data

The endometrial safety in Study 0713D2-309-US was assessed with endometrial biopsies at cycles 6 and 13. The procedure for determining final diagnosis complied with the proposed revisions to the 1995 HRT Guidance document which is entitled "Guidance for Industry-Clinical Evaluation of Estrogen- and Estrogen/Progestin Drug Products Used for Hormone Replacement Therapy in Postmenopausal Women". Two thousand one hundred fifty three (2,153) subjects were included in the primary analysis of endometrial hyperplasia and cancer by cycle 13. The Sponsor's analysis showed no endometrial cancer occurring during the course of the study. However, the clinical review led to a reclassification of two cases of hyperplasia (per the Sponsor) to endometrial carcinoma (per the clinical reviewers). The cycle 5-7 endometrial biopsy of subject 30924-0011 (0.3 mg CE) was read as complex hyperplasia with atypia by study pathologist 1 and endometrial adenocarcinoma, focal by study pathologist 2. The third adjudicating study pathologist (specified in the protocol to read slides where there was a disagreement in the diagnosis of hyperplasia) did not read the slides. The patient withdrew from the study and had her slides re-read by an unblinded gynecologic oncologist, who agreed with the diagnosis of study pathologist 2. The Sponsor assigned this case as hyperplasia. However, because the third assessor was outside of the study and was not blinded, this diagnosis should not be considered. Taking into consideration the most conservative diagnosis ("worst case") between pathologist 1 and pathologist 2, the clinical reviewing team reclassified this diagnosis as endometrial adenocarcinoma. The cycle 5-7 endometrial biopsy of subject 30912-0049 (0.45 mg CE/ 1.5 mg MPA) was read as complex hyperplasia with atypia in a polyp by pathologist 1, endometrial adenocarcinoma involving an endometrial polyp by pathologist 2, and endometrial adenocarcinoma in a polyp by pathologist 3. The Sponsor assigned this case as hyperplasia. The clinical review team reclassified this case as endometrial adenocarcinoma following the HRT Guidance document recommendation that the majority diagnosis, two of the three pathologists, is the accepted final diagnosis. A third case was also reviewed for difficulty in the diagnosis. The

cycle 5-7 endometrial biopsy of subject 30908-0003 (0.3 mg CE/1.5 mg MPA) was read as back-to-back glandular architecture, can not rule out hyperplasia by pathologist 1, complex hyperplasia with atypia by pathologist 2 and atypical glandular proliferation by pathologist 3. All three pathologists disagreed as to diagnostic severity. The Sponsor assigned this subject as hyperplasia. Following the proposed revised HRT Guidance scheme, since all three pathologists essentially disagreed, the clinical review team considered the worst case scenario and assigned this subject a diagnosis of complex hyperplasia with atypia. The rate of endometrial hyperplasia for all treatment groups is shown below in Table 4, modified from MO Table 7.

Table 4 Incidence of Endometrial Hyperplasia at Cycle 13,

Treatment	n	Total number of Hyperlasias	Hyperplasia rate (one-sided 95% CI)	p-value vs. CE alone
0.625 mg CE	249	20	8.03 (0, 11.5)	N/A.
0.625 mg CE/2.5 mg MPA	278	0	0.00 (0, 1.1)	<0.001
0.45 mg CE	279	9	3.23 (0, 5.6)	N/A
0.45 mg CE/2.5 mg MPA	273	0	0.00 (0, 1.1)	0.004
0.45 mg CE/1.5 mg MPA	272	0	0.00 (0, 1.2)	0.004
0.3 mg CE	269	0	0.00 (0, 1.1)	N/A
0.3 mg CE/ 1.5 mg MPA	272	1	0.37 (0, 1.8)	1.00
Placebo	261	0	0.00 (0,1.2)	

The occurrence of one case of endometrial adenocarcinoma in a CE alone treatment arm (0.3 mg CE) is not higher than that seen in other large prospective controlled clinical trials. Although the occurrence of an endometrial cancer is rare in controlled clinical trials for combination CE/progestin trials, zero to one case of endometrial adenocarcinoma have been reported in estrogen/progestin treatment groups for other large, controlled clinical trials of HRT products. The data presented above demonstrate a low rate of endometrial hyperplasia in CE/MPA treatment arms with 1 case only of endometrial hyperplasia demonstrated in one of the combination CE/MPA arms (0.3 mg CE/ 1.5 mg MPA). Three of the 4 combination CE/MPA treatment arms showed no cases of hyperplasia. There is a dose-dependent response in endometrial hyperplasia rates in the CE alone treatment groups (when considering hyperplasia only and not the single case of endometrial cancer that occurred in a CE alone treatment group). The 0.625 mg CE group produced the highest incidence of endometrial hyperplasia and the 0.3 mg CE group produced the lowest incidence.

In the 4-Month Safety Update only subjects who reported endometrial hyperplasia as an adverse event were included. As such this reporting may not represent all cases of hyperplasia that occurred during the reporting period. The Sponsor reported 8 cases of endometrial hyperplasia as adverse events. The reviewer identified 6 additional cases of endometrial hyperplasia. Fourteen cases of endometrial hyperplasia occurred during the reporting period for the 4-Month Safety Update, between December 23, 1999 and August 2, 2000. Of these 14 cases, 8 cases were in the 0.625 mg CE group, 5 cases in the 0.45 mg CE group and 1 case in the 0.3 mg CE group. No cases of endometrial carcinoma were reported in the 4-Month Safety Update.

Three cases of simple hyperplasia without atypia were reported in the Second Safety Update. One case of hyperplasia occurred in the 0.625 mg CE treatment group and two cases of hyperplasia occurred in the 0.45 mg CE treatment group. No cases of endometrial adenocarcinoma were reported in the Second Safety Update.

In total, 47 subjects across the 8 treatment arms developed endometrial hyperplasia and 2 subjects developed endometrial carcinoma. Overall the incidence of endometrial hyperplasia in Study 0713D2-309-US is acceptable and low.

Bleeding profiles were summarized according to entries recorded by the subject in daily diary cards. The percentage of subjects in all treatment groups who became amenorrheic and remained so throughout the study year increased with each consecutive cycle. Overall, subjects in the CE and CE/MPA treatment groups exhibited fewer consecutive cycles of amenorrhea than subjects on placebo. As the dosage strength of the CE group decreased the percentage of subjects without bleeding or spotting increased. The highest CE dosage strength (0.625 mg) exhibited fewer cycles without any bleeding or spotting than the 0.45 and 0.3 mg dosage strengths. The lowest CE dosage strength and placebo were not different at any time point analyzed. The bleeding profile of the 0.45 CE group is acceptable

A total of 266 subjects (10%) discontinued the study due to adverse events. The rate of discontinuations due to adverse events is not unusual for this size study and does not raise concern for safety. The 4-Month Safety Update, which also includes data from year 2 subgroup subjects, covers the time period between December 24, 1999 and August 2, 2000. Twenty-one (21) additional subjects discontinued the study due to adverse events or adverse reaction. The Second Safety Update, which was submitted on May 15, 2001, covers the period between August 3, 2000 through April 2, 2001. Three (3) additional subjects withdrew from the study because of adverse events during this time period

Eighty-nine percent (89%, n=2,386) of the 2,673 subjects treated in Study 0713D2-309-US reported treatment emergent adverse events. Overall, treatment emergent adverse events were similar between the 0.45 mg CE treatment group and the placebo treatment group. Headaches were the most frequently reported treatment emergent adverse event for the 0.45 mg CE treatment group and the placebo treatment group, 32% and 28%, respectively. Breast pain occurred more frequently in the 0.45 mg CE treatment group (12%) than in the placebo treatment group (9 %). Vaginal hemorrhage (the COSTART term that includes vaginal bleeding, intermittent vaginal bleeding and excessive or heavy vaginal bleeding) occurred more frequently in the 0.45 mg CE treatment group (4%) than in the placebo treatment group (0%). The 4-Month Safety Update reports on 133 subjects (21% of the 634 subjects who entered cycle 14) with treatment emergent adverse events. Fifty-four (54) subjects reported treatment emergent adverse events between August 3, 2000 and April 2, 2001, the time period covered by the Second Safety Update. At the time of this review, the 2nd year of the osteoporosis substudy is now completed and unblinded; the final report is still in preparation.

Based on the data reported in the NDA, women treated with CE alone (0.625 mg, 0.45 mg and 0.3 mg) in general had a more favorable increase in HDL-C and HDL_2-C concentrations than women treated with CE/MPA (0.625 mg CE/2.5 mg MPA, 0.45 mg CE/2.5 mg MPA, 0.45 mg CE/1.5 MPA and 0.3 mg CE/1.5 mg MPA). The decrease in LDL-C concentrations was similar in women treated with CE alone and CE/MPA combinations.

Conclusions and Recommendations

The safety and efficacy data presented in S-115 support the approval of the 0.45 mg CE strength for the treatment of VMS and VVA associated with the menopause. I concur with the recommendation of the primary clinical reviewer that the 0.45mg strength can be approved, pending an acceptable cGMP status of the manufacturing facilities and satisfactory resolution of labeling issues.

Suggested labeling revisions are as follows:

The **WARNINGS** section, 1. [ ] malignant neoplasms, a. Endometrial cancer subsection has been revised to [ ]

In addition the **WARNINGS** section has been changed to incorporate revised language under the Breast cancer and Thromboembolic [ ] subsections that has previously been recommended to the Sponsor in NDA 4-782/ Supplements [ ]

The **PRECAUTIONS** section has been changed to incorporate the Addition of a progestin when woman has not had a hysterectomy subsection, and to update the Cardiovascular [ ] subsection in accordance with the Division's recommendations previously provided to the Sponsor in NDA 4-782/Supplement [ ]

The Pediatric Use subsection has been updated, and a Geriatric Use subsection has been added.

The **DOSAGE AND ADMINISTRATION** section has been change to the following:

[ ]

The Patient Information Insert has been revised in accordance with the plain language initiative

Shelley R. Slaughter, MD, Ph.D.

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

/s/

Shelley Slaughter
7/31/01 12:09:57 PM
MEDICAL OFFICER

Daniel A. Shames
7/31/01 01:42:57 PM
MEDICAL OFFICER

Filing Memorandum
Division of Reproductive and Urologic Drug Products

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sNDA 4-782/S-115

Trade Name:	**Premarin®**
Generic Name:	**Conjugated estrogens (CE)**
Sponsor:	**Wyeth-Ayerst Research** **P.O. Box 8299** **Philadelphia, PA 19101-8299**
Submission Date:	**July 31, 2000**
Date Received:	**July 31, 2000**
Indications:	**• Treatment of moderate to severe vasomotor symptoms associated with the menopause** **• Treatment of vulvar and vaginal atrophy**
Dose Form:	**0.45 mg tablet**
Treatment Schedule:	**Continuous with no interruption in therapy, or in cyclic regimens such as 25 days on drug followed by five days off drug as is medically appropriate on an individualized basis**
User Fee Goal Date:	**May 31, 2001**
Division Goal Date:	**May 31, 2001**
Filing Date:	**September 29, 2000**
Medical Reviewer:	**Theresa H. van der Vlugt, M.D., M.P.H.**

Submission Resume

In this submission, Wyeth-Ayerst proposes the 0.45 mg Premarin® Tablet for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause and the treatment of vulvar and vaginal atrophy.

The submitted clinical trial conducted (and continuing), Study 0713D2-309-US (the HOPE Study), was undertaken to satisfy a post-approval commitment to the FDA for Prempro™ 2.5 (approved 1994) to determine the lowest effective dose of CEE/MPA for the prevention of osteoporosis. Study 0713D2-309-US was also submitted in support of [ ] for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause.

This 8 arm, 24-month, double-dummy clinical trial includes 2,673 postmenopausal women who received one of the 4 following doses of CE plus MPA: 0.625 mg/2.5 mg MPA, 0.45 mg CE/2.5 mg MPA, 0.45 mg CE/1.5 mg MPA, and 0.30 CE/1.5 mg MPA; the corresponding doses of CE alone (0.625 mg, 0.45 mg, and 0.30 mg); and placebo. Subjects were randomly assigned doses and were instructed to take 2 tablets of the study medication daily (one active tablet and one matching placebo tablet or two matching placebo tablets) and one Caltrate tablet daily (elemental calcium, 600 mg) at approximately the same time each day. The Hope Study is comprised of a basic study (12 months, 13 cycles) and a metabolic/osteoporosis substudy (24 months, 26 cycles).

The Sponsor submitted a plan for an interim analysis of the HOPE Study data at 1-year to the Division. On December 9, 1999 the Sponsor was notified that the proposed statistical plan for an interim analysis was appropriate and that appropriate precautions were being taken to assure that the study blind was maintained for the osteoporosis and metabolism substudy.

The 12-month data from completed study year 1 (2153 subjects, 1,553 subjects in the basic study and 599 subjects ongoing in the metabolic/osteoporosis substudy) submitted in this sNDA application supports the

safety and efficacy of the 0.45 mg dose in relieving moderate-to-severe hot flushes and vulvar and vaginal atrophy. The Sponsor anticipates submitting the full 2-year study data for a prevention of osteoporosis indication.

The primary efficacy measurement for study year 1 is an assessment of the incidence of endometrial hyperplasia, made by endometrial biopsies conducted at baseline, 6 months and 12 months. Vasomotor symptoms and vaginal maturation indexes, assessed by evaluation of daily diaries and vaginal cytology smears, are secondary efficacy measurements. Study subjects were enrolled without regard to the frequency and severity of hot flushes at baseline.

One Phase 1 bioavailability study is included in the sNDA application: Phase 1 Study 0713D2-119-US conducted in 31 postmenopausal women (2 x 0.45 mg CE, identical to the marketed formulation except for color coat which is white).

Fileability of Supplemental NDA 4-782/S-115

Supplemental NDA 4-782/S-115 is fileable.

Review Issues

1) Large variability in study center enrollment (57 of 58 centers enrolled from 3 to 147 subjects; 1 center (Center 30952) was found by the Sponsor not to be in compliance with Good Clinical Practice (GCP) leading to early termination of the study site and exclusion of all data from this site.
2) Patients were enrolled in the study if they had a serum estradiol concentration of $\leq$ 184 pmol/L (equivalent to $\leq$ 50 pg/ml), FSH concentration of $\geq$ 30 IU/L
3) Absence of baseline inclusion criteria for 7-8 moderate-to-severe hot flushes per day or 50-60 per week. MSVS substudy population represents only 9% of the total study population (240/2673). Total number of evaluable subjects is 32 in the 0.45 mg CE group and 28 in the placebo group.
4) An analysis of the change from baseline for the frequency and severity of hot flushes was not performed. Instead, the comparisons to placebo were performed on the observed number and severity of hot flushes with baseline as a covariant. No procedure for carrying forward missing data was implemented.
5) Adverse events of note include 8 reports of breast cancer (1 post-study), 7 cases of vascular thromboses (CVA, MI, DVT, pulmonary embolism) including one case with a transient ischemia attack (TIA is not reported in current labeling, a 15-day IND Safety Report was sent).

Attachment: 45-Day Filing Meeting Checklist
Cc: NDA 20-527 Division File
HFD-580/DMoore/SSlaughter/TvanderVlugt

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
7/11/01 12:01:30 PM
MEDICAL OFFICER
Filing memo previously sent to document room now included in DFS for c
ompleteness.

Shelley Slaughter
7/11/01 01:50:23 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 04-782/S-115 & S-130

CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF **SUPPLEMENT**

1. **ORGANIZATION:** DRUDP HFD-580
2. **NDA NUMBER:** 4-782/SE2-115
3. **SUPPLEMENT NUMBERS/DATES:**
   Letterdate: 31-JUL-2000
   Stampdate: 31-JUL-2000
4. **AMENDMENTS/REPORTS/DATES:**
   Letterdate: See list on page 4
   Stampdate:
5. **RECEIVED BY CHEMIST:** 07-AUG-2000

6. **APPLICANT NAME AND ADDRESS:**
   Wyeth-Ayerst Laboratories
   P.O. Box 8299
   Philadelphia, PA 19101-8299

7. **NAME OF DRUG:**
   Premarin Tablets

8. **NONPROPRIETARY NAME:**
   Conjugated estrogens

9. **CHEMICAL NAME/STRUCTURE:**
   see USP 24

10. **DOSAGE FORM(S):**
    Tablets

11. **POTENCY:**
    0.3, **0.45**, 0.625, 0.9, 1.25, 2.5 mg

12. **PHARMACOLOGICAL CATEGORY:**
    Estrogen/Hormone replacement therapy

13. **HOW DISPENSED:**
    RX

14. **RECORDS & REPORTS CURRENT:**
    Yes

15. **RELATED IND/NDA/DMF:**
    none

16. **SUPPLEMENT PROVIDES FOR:**
    One new dosage strength drug product tablet, 0.45 mg.

17. **COMMENTS**
    This efficacy supplement provides for a new dosage strength tablet of conjugated estrogens (CE) [0.45 mg] in a continuous regimen for the treatment of moderate to severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy. The drug substance is identical to that in the approved dosage strength tablets and the drug product manufacturing process is identical to the approved process.

18. CONCLUSIONS AND RECOMMENDATIONS:

From a Chemistry, Manufacturing and Controls point of view this NDA is approvable. The NDA may be approved pending an acceptable cGMP status of the manufacturing facilities and satisfactory resolution of the CMC labeling issues.

19. REVIEWER NAME	**SIGNATURE**	**DATE COMPLETED**
David T. Lin, Ph.D. Review Chemist		06-JUL-2001

cc: Original: NDA 4-782/SE2-115
HFD-580/Division File
HFD-580/DMoore
HFD-580/MRhee/DLin

INIT by MJ Rhee

Filename: S4782.115 (doc)

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Chemistry Review

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/s/

David T. Lin
7/6/01 10:22:05 AM
CHEMIST
AE recommendation pending satsfactory cGMP status and satisfactory res
olution of labeling issues.

Moo-Jhong Rhee
7/9/01 02:55:31 PM
CHEMIST
I concur

CHEMIST REVIEW #1 Addendum
OF **SUPPLEMENT**

1. **ORGANIZATION:** DRUDP HFD-580
2. **NDA NUMBER:** 4-782/SE2-115
3. **SUPPLEMENT NUMBERS/DATES:**
   Letterdate: 31-JUL-2000
   Stampdate: 31-JUL-2000
4. **AMENDMENTS/REPORTS/DATES:**
   Letterdate: See list on page 4
   Stampdate:
5. **RECEIVED BY CHEMIST:** 07-AUG-2000

6. **APPLICANT NAME AND ADDRESS:**
   Wyeth-Ayerst Laboratories
   P.O. Box 8299
   Philadelphia, PA 19101-8299

7. **NAME OF DRUG:**
   Premarin Tablets

8. **NONPROPRIETARY NAME:**
   Conjugated estrogens

9. **CHEMICAL NAME/STRUCTURE:**
   see USP 24

10. **DOSAGE FORM(S):**
    Tablets

11. **POTENCY:**
    0.3, **0.45**, 0.625, 0.9, 1.25, 2.5 mg

12. **PHARMACOLOGICAL CATEGORY:**
    Estrogen/Hormone replacement therapy

13. **HOW DISPENSED:**
    RX

14. **RECORDS & REPORTS CURRENT:**
    Yes

15. **RELATED IND/NDA/DMF:**
    none

16. **SUPPLEMENT PROVIDES FOR:**
    One new dosage strength drug product tablet, 0.45 mg.

17. **COMMENTS**
    This addendum to Chemistry Review #1 is an update on the status of the manufacturing facilities inspections. The District Office has issued a Withhold recommendation for the Wyeth drug product manufacturing facility in New York. The Office of Compliance has concurred with their recommendation for the New York site and issued an overall Withhold recommendation for this supplement (see EER in Appendix A).

18. CONCLUSIONS AND RECOMMENDATIONS:

From a Chemistry, Manufacturing and Controls point of view this NDA is approvable. The NDA may be approved pending an acceptable cGMP status of the manufacturing facilities and satisfactory resolution of the CMC labeling issues.

19. REVIEWER NAME	**SIGNATURE**	**DATE COMPLETED**
David T. Lin, Ph.D. Review Chemist		26-JUL-2001

cc: Original: NDA 4-782/SE2-115
HFD-580/Division File
HFD-580/DMoore
HFD-580/MRhee/DLin

INIT by MJ Rhee

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Chemistry Review #1 Addendum

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/s/

David T. Lin
7/26/01 02:33:43 PM
CHEMIST
Addendum to Chemistry Review #1 with final OC recommendation.

Moo-Jhong Rhee
7/26/01 04:41:38 PM
CHEMIST
I concur

CHEMIST REVIEW #1 Addendum #1
OF **SUPPLEMENT**

1. **ORGANIZATION:** DRUDP HFD-580
2. **NDA NUMBER:** 4-782/SE2-115
3. **SUPPLEMENT NUMBERS/DATES:**
   Letterdate: 31-JUL-2000
   Stampdate: 31-JUL-2000
4. **AMENDMENTS/REPORTS/DATES:**
   Letterdate: See list on page 4
   Stampdate:
5. **RECEIVED BY CHEMIST:** 07-AUG-2000

6. **APPLICANT NAME AND ADDRESS:**
   Wyeth-Ayerst Laboratories
   P.O. Box 8299
   Philadelphia, PA 19101-8299

7. **NAME OF DRUG:**
   Premarin Tablets

8. **NONPROPRIETARY NAME:**
   Conjugated estrogens

9. **CHEMICAL NAME/STRUCTURE:**
   see USP 24

10. **DOSAGE FORM(S):**
    Tablets

11. **POTENCY:**
    0.3, **0.45**, 0.625, 0.9, 1.25, 2.5 mg

12. **PHARMACOLOGICAL CATEGORY:**
    Estrogen/Hormone replacement therapy

13. **HOW DISPENSED:**
    RX

14. **RECORDS & REPORTS CURRENT:**
    Yes

15. **RELATED IND/NDA/DMF:**
    none

16. **SUPPLEMENT PROVIDES FOR:**
    One new dosage strength drug product tablet, 0.45 mg.

17. **COMMENTS**
    This addendum #1 to Chemistry Review #1 is an update on the status of the manufacturing facilities inspections. The overall recommendation from the Office of Compliance still remains a Withhold (see Addendum to Chemistry Review #1 dated 7/26/01). However, in addition to a Withhold recommendation for the New York facility, the Puerto Rico facility has now been issued a Withhold recommendation (see EER in Appendix A).

18. CONCLUSIONS AND RECOMMENDATIONS:

From a Chemistry, Manufacturing and Controls point of view this NDA is approvable. The NDA may be approved pending an acceptable cGMP status of the manufacturing facilities and satisfactory resolution of the CMC labeling issues.

19. REVIEWER NAME	**SIGNATURE**	**DATE COMPLETED**
David T. Lin, Ph.D. Review Chemist		30-JUL-2001

cc: Original: NDA 4-782/SE2-115
HFD-580/Division File
HFD-580/DMoore
HFD-580/MRhee/DLin

INIT by MJ Rhee

Filename: S4782ad1.115 (doc)

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Chemistry Review#1 Addendum#1

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/s/

David T. Lin
7/30/01 01:56:48 PM
CHEMIST
Addendum #1 to Chemistry Review #1, EER update.

Moo-Jhong Rhee
7/30/01 01:59:37 PM
CHEMIST

CHEMIST REVIEW #2
OF **SUPPLEMENT**

1. **ORGANIZATION:** DRUDP HFD-580
2. **NDA NUMBER:** 4-782/SE2-115
3. **SUPPLEMENT NUMBERS/DATES:**
   Letterdate: 31-JUL-2000
   Stampdate: 31-JUL-2000
4. **AMENDMENTS/REPORTS/DATES:**
   Letterdate: See list on page 4
   Stampdate: See list on page 4
5. **RECEIVED BY CHEMIST:** 5-NOV-2002

6. **APPLICANT NAME AND ADDRESS:**
   Wyeth-Ayerst Laboratories
   P.O. Box 8299
   Philadelphia, PA 19101-8299
   (484)-865-3749

7. **NAME OF DRUG:**
   Premarin Tablets

8. **NONPROPRIETARY NAME:**
   Conjugated estrogens

9. **CHEMICAL NAME/STRUCTURE:**
   Conjugated estrogens (CE) – Please refer to USP 25.

10. **DOSAGE FORM(S):**
    Tablets

11. **POTENCY:**
    0.3 mg, *0.45 mg*, 0.625 mg, 0.9 mg, 1.25 mg, 2.5 mg

12. **PHARMACOLOGICAL CATEGORY:**
    Estrogen/Hormone replacement therapy

13. **HOW DISPENSED:**
    Rx

14. **RECORDS & REPORTS CURRENT:**
    Yes

15. **RELATED IND/NDA/DMF:**
    None

16. **SUPPLEMENT PROVIDES FOR:**
    One new dosage strength of the drug product, 0.45 mg

17. **SPECIAL PRODUCTS: YES _X_ NO ___** (A form for this NDA has already been submitted).

18. **COMMENTS**

This efficacy supplement provides for an additional dosage strength (0.45 mg) for tablets of conjugated estrogens (CE), in a continuous regimen for the treatment of moderate to severe vasomotor symptoms associated with menopause and treatment of vulvar and vaginal atrophy. The drug substance is identical to that in the approved dosage strength tablets, and the drug product manufacturing process is identical to the approved process.

This review covers materials submitted by the Sponsor (please refer to the list on page 4) as a complete response to the approvable letter issued by the Agency on 31-JUL-2001 for NDA 4-782/SE2-115.

NDA 4-782/SE2-115 was deemed approvable from a CMC standpoint in the first review cycle, based on GMP compliance issues as well as minor proposed labeling changes (see Chemistry Review #1 dated July 6, 2001, by Dr. David T. Lin). These items are discussed in the applicable sections of the attached review.

19. **CONCLUSIONS AND RECOMMENDATIONS:**

From a CMC standpoint, this supplement is acceptable and may be approved.

20. **REVIEWER NAME**	**SIGNATURE**	**DATE COMPLETED**
Sarah Pope		26-Mar-2003

cc: Original: NDA 4-782/SE2-115
HFD-580/Division File
HFD-580/KSherrod
HFD-580/DLin/SPope

Filename: NDA4782S115.doc

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Chemistry Review #2

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/s/

Sarah Pope
4/18/03 10:35:25 AM
CHEMIST

David T. Lin
4/18/03 11:14:44 AM
CHEMIST
I concur.

Summary of Chemistry Review of NDA 4-782, SE-115 (Premarin)

A. Drug Substances:

Conjugated estrogens are natural estrogens derived from horse urine, which have been used for Premarin for more than 50 years, and no change has been introduced in the drug substance. The drug substance is manufactured by both Wyeth Laboratories, Inc., in Rouses Point, NY and Ayerst Organics Inc., Manitoba, CA, and they are ***in compliance*** to cGMP.

B. Drug Product:

This proposed drug product is a **new strength tablet** containing 0.45mg of conjugated estrogens, and it is manufactured in accordance with the procedures of previously approved 0.3mg and 0.625mg tablets using the **same excipients** in the tablet-core and same[ ] as well as [ ] [ ] Two **salient differences** are; 1) the **amounts of conjugated estrogens** and [ ] [ ] to make the tablets identical in weight, and 2) the **color** coat containing **FD&C Blue #2.**

They are manufactured by Ayerst Laboratories, Rouses Point, NY and Wyeth-Pharmaceuticals Company, Puerto Rico, and ***the former is not in compliance to cGMP.***

Based on this, the Office of Compliance made an overall recommendation of "**WITHHOLD**" for the application.

The quality of the new tablets is controlled by the **same specifications** for 0.3mg and 0.625mg tablets, except for the "appearance" specification, which specifies color of the tablet.

The tablets are packaged into **blister packs** [ ] and [ ] **bottles** (100 counts), and they are considered to be **adequate** for protecting the product during the shelf-life.

Based on **3 primary stability batch** data (12 months at 25°C/60%RH and 6 months at 40°C/75%) together with **long term stability** experience from the previously approved 0.3mg and 0.625mg tablets, the proposed **expiry date of 24-month is granted.**

C. Conclusion and Recommendation:

From chemistry, manufacturing, and controls point of view, this NDA is ***approvable*** pending satisfactory GMP status and resolution of some minor labeling issues.

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
For the Division of Reproductive and Urologic Drug Products
DNDC II, Office of New Drug Chemistry

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/s/

Moo-Jhong Rhee
7/27/01 02:31:49 PM
CHEMIST

Addendum to Summary of Chemistry Review of NDA 4-782, SE-115
(Premarin)

A. Drug Substances:

Same as the preceding Summary

B. Drug Product:

As of July 30, 2001, the recommendation from the Office of Compliance on the cGMP status of Wyeth-Pharmaceuticals Company, Puerto Rico, has been changed from "Acceptable" to "Withhold".

C. Conclusion and Recommendation:

Same as the preceding summary

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
For the Division of Reproductive and Urologic Drug Products
DNDC II, Office of New Drug Chemistry

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/s/

Moo-Jhong Rhee
7/30/01 01:24:38 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 04-782/S-115 & S-130

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA:	04-782/S-115
Name of Drug:	Premarin (conjugated estrogens, USP)
NDA:	20-527/S-017
Name of Drug:	Prempro (conjugated estrogens and medroxyprogesterone acetate combination tablets)
Applicant:	Wyeth-Ayerst Research
Indication:	Protection of the endometrium
Documents Reviewed:	04-782/S-105: Volumes 1-3, 71 20-527/S-017: Volumes 1-3, 71
Medical Reviewer:	Theresa van der Vlugt, M.D. (HFD-580)
Statistical Reviewer:	Lisa A. Kammerman, Ph.D. (HFD-715)

Background:

Calculations of one-sided 95% confidence intervals for rates of hyperplasia, and for rates of carcinoma are the focus of this review. The medical reviewer requested these.

The data come from the HOPE study, which was submitted to both of the supplemental NDAs shown above. The supplements contain two-sided confidence intervals for hyperplasia rates. The medical reviewer reclassified one case of endometrial hyperplasia as a carcinoma. The applicant did not identify any cases of carcinoma.

The primary objective of Study Year 1 was to evaluate the efficacy of lower doses of CE and MPA in reducing the incidence of endometrial hyperplasia associated with the use of unopposed estrogen. Of the 2,805 women randomized, endometrial hyperplasia results for 2,153 women were analyzed. These women had biopsies positive for endometrial hyperplasia during the first 14 cycles, or had a biopsy (negative or positive) done during cycles 12 through 14.

Confidence intervals

The confidence intervals on the next page are exact Clopper-Pearson intervals, as calculated by
[ ]

Table 1 shows the results for the incidence of endometrial hyperplasia at 1 year; Table 2 shows the carcinoma results.

Table 1: Incidence and one-sided 95% CIs of endometrial hyperplasia at Cycle 13

Treatment:	N	Total number of hyperplasias	One-sided 95% confidence interval
Group A: (0.625 CE)	249	20	(0, 11.5%)
Group B: (0.625 CE/2.5 MPA)	278	0	(0, 1.1%)
Group C: (0.45 CE)	279	9	(0, 5.6%)
Group D; (0.45 CE/2.5 MPA)	273	0	(0, 1.1%)
Group E: (0.45 CE/1.5 MPA)	272	0*	(0, 1.2%)
Group F: (0.3 CE)	269	1	(0, 1.8%)
Group G: (0.3 CE/1.5 MPA)	272	1	(0, 1.8%)
Group H: (Placebo)	261	0	(0, 1.2%)

Source: Columns 1, 2, and 3 are taken from Table 9.2.2.1A in the Study Report. I calculated the confidence intervals.

* The study report indicated 1 endometrial hyperplasia. The medical reviewer reclassified the case as a carcinoma.

Table 2: Incidence and one-sided 95% CIs of endometrial carcinoma at Cycle 13

Treatment:	N	Total number of Carcinomas	One-sided 95% confidence interval
Group A: (0.625 CE)	249	0	(0, 1.3%)
Group B: (0.625 CE/2.5 MPA)	278	0	(0, 1.1%
Group C: (0.45 CE):	279	0	(0, 1.1%)
Group D; (0.45 CE/2.5 MPA)	273	0	(0, 1.1%)
Group E: (0.45 CE/1.5 MPA)	272	1*	(0, 1.8%)
Group F: (0.3 CE)	269	0	(0, 1.2%)
Group G: (0.3 CE/1.5 MPA)	272	0	(0, 1.1%)
Group H: (Placebo)	261	0	(0, 1.2%)

Source: Columns 1 and 2 are taken from Table 9.2.2.1A in the Study Report. I calculated the confidence intervals.

* The medical reviewer reclassified this case as a carcinoma. The applicant originally identified it as an endometrial hyperplasia.

Lisa A. Kammerman, Ph.D.
Mathematical Statistician, Biometrics II

Concur: Edward Nevius, Ph.D.
Division Director, Biometrics II

cc:
HFD-580/Dr. Van Der Vlugt
HFD-580/Dr. Slaughter
HFD-580/Dr. Allen
HFD-580/Ms. Moore
HFD-715/Ms. Farr
HFD-715/Dr. Kammerman
HFD-715/Dr. Nevius
HFD-715/Dr. Welch
HFD-700/Dr. Anello

/s/

Lisa A. Kammerman
3/18/01 06:24:12 PM
BIOMETRICS
This is my review of the hyperplasia results.

S. Edward Nevius
3/18/01 06:32:32 PM
BIOMETRICS
Concur with review.

STATISTICAL REVIEW AND EVALUATION

NDA:	04-782/S-115
Name of Drug:	Premarin (conjugated estrogens, USP)
NDA:	20-527/S-017
Name of Drug:	Prempro (conjugated estrogens and medroxyprogesterone acetate combination tablets)
Applicant:	Wyeth-Ayerst Research
Indication(s):	Treatment of moderate to severe vasomotor symptoms associated with menopause
Documents Reviewed:	04-782/S-105: Volumes 1-3, 71 20-527/S-017: Volumes 1-3
Medical Reviewer:	Theresa van der Vlugt, M.D./HFD-580
Statistical Reviewer:	Shahla S. Farr, M.S./HFD-715

Introduction:

Both supplemental NDAs include the same prospective, double blind, randomized study (Protocol 0713D2-309-US, the HOPE study) and, therefore, are reviewed together in this document.

The applicant is seeking approval of a new low dose of Premarin (0.45 mg) tablets, administered alone[ ] for the treatment of moderate to severe vasomotor symptoms (MSVS) associated with menopause. These requests are in the Premarin supplement.

The applicant is also seeking approval of[ ] new lower combination doses of CE/MPA (.45 mg CE/1.5 mg MPA)[ ] for reducing the incidence of endometrial hyperplasia associated with the use of unopposed estrogen, and for the treatment of MSVS. CE/MPA is administered in a continuous combined regimen. These requests are in the Prempro supplement.

The treatment of MSVS is the focus of this review.

Reviewer's Comments: The sponsor has conducted only one study. In general two adequate and well-controlled Phase 3 clinical trials are needed for approval, so that the results can be reproduced. It is difficult to confirm the results and conclusions based only on one study.

Study Description:

The HOPE study is a placebo-controlled study done in postmenopausal women to evaluate the efficacy and safety of three different strengths of CE alone tablets and four different strengths of combination CE/MPA tablets in reducing the incidence of endometrial hyperplasia associated with the use of unopposed estrogen. A secondary objective is to evaluate the efficacy of CE alone and combination CE/MPA tablets, compared with placebo, in treating MSVS.

The study contains two parts, a basic study and an osteoporosis and metabolic substudy. The basic study is 1 year long (13 cycles); the substudy is 2 years long (26 cycles). The basic study is the focus of these supplemental NDAs.

HOPE is an 8-arm, double-blind, double-dummy, placebo/active-drug-controlled, multicenter outpatient study of lower-dose CE and CE/MPA tablets conducted in healthy postmenopausal women with an intact uterus. Although MSVS was not an entry criterion, the study report states "every effort was made to recruit patients who experienced an average of at least 7 to 8 MSVS per day" (page 41 of study report). All patients were required to undergo a minimum 8-week pre-study washout (women in the basic study) or 12-week week pre-study washout (women in the substudy) for prior estrogen, progestin, or androgen therapy.

A total of 2,805 women were randomized to one of eight study arms. A total of 2,673 were patients who received either active medication or placebo:

1) 0.625 CE (n=348) ("A")
2) 0.625 CE/2.5 MPA (n=331) ("B")
3) 0.45 CE (n=338) ("C")
4) 0.45 CE/2.5 MPA (n=340) ("D")
5) 0.45 CE/1.5 MPA (n=331) ("E")
6) 0.3 CE (n=326) ("F")
7) 0.3 CE/1.5 MPA (n=327) ("G")
8) Placebo (n=332) ("H")

Because MSVS was not an entry criterion, the analysis of MSVS was restricted to those women with at least 7 MSVS recorded on each of the last 7 days of the screening diary card prior to randomization, or at least 50 MSVS on the last 7 days combined. Thus a subgroup of subjects with moderate to severe vasomotor symptoms was analyzed for the MSVS indication (n=241). This group is called the "EE population".

Efficacy Endpoints:
The efficacy endpoints were **the frequency of hot flushes and severity of hot flushes**. The patients recorded each on the daily diary cards. The average daily number and average daily severity of hot flushes were evaluated by week for weeks 1 through 12, and by cycle for cycles 1 through 13. Baseline values for hot flushes were determined from the last 7 days of screening diary card data prior to study medication intake. Baseline and on-therapy averages of the number of hot flushes were calculated as the sum of the number of hot flushes on each day / number of days with data. Severity of hot flushes was recorded as mild (1), moderate (2) or severe (3). Severity was calculated as the sum of the daily severity scores / number of days with data, where the daily severity score was calculated as ((number of mild hot flushes) X 1 + (number of moderated hot flushes) X 2 + (number of severe hot flushes) X 3) / total number of hot flushes on that day. Any day with no flushes was included in the calculations, with a severity of zero. The days with all 3 categories missing were excluded from the calculations.

Vasomotor symptoms were analyzed by an analysis of covariance (ANCOVA) for comparisons between groups, and the least significant difference (LSD) procedure for pairwise comparisons. The baseline mean of VSMS was used as the covariate in the ANCOVAs.

Demographics and Baseline Characteristics:
According to the sponsor, the treatment groups were comparable in all demographic and baseline characteristics for the women evaluated for endometrial hyperplasia.

There were no significant differences among the treatment groups in the number of hot flushes at baseline.

*Reviewer's Comments: This comparability of the arms in regards to the demographics and baseline characteristics was assessed only for the patients evaluable for efficacy with respect to **endometrial hyperplasia**. The demographics and baseline characteristics for the sub-population under the study for **vasomotor symptoms** were not evaluated.*

Efficacy Results:

The population that was appropriate for the indication, and that was analyzed for the VSMS endpoint was:

> *Efficacy Evaluable (EE) by Week*: All patients randomly assigned to the study, recorded taking study medication, and had at least 7 moderate to severe baseline hot flushes recorded on each of the last 7 days of the screening diary card, or at least 50 moderate to severe hot flushes on the last 7 days combined. At least 5 of 7 days' data had to be available at screening and for an on-therapy week to be included in these analyses. Weeks 1 though 12 were assessed. No procedure for imputing missing data was implemented.

The follwing table is a summary tabulation of the number of hot flushes, adjusted mean and comparisons between the active treatment groups and placebo group in the EE population for weeks 1, 4, 8 and 12.

TABLE: Summary Tabulation Of The Number Of Hot Flushes, Adjusted Mean And The P Values For The Comparisons Between The Active Treatment Groups And Placebo Group In The EE Population For Weeks 1, 4, 8 and 12

Treatment:	N	Adjusted Mean ± SE	P-Value vs. Placebo
Group A: (0.625 CE):			
Week-1	27	8.11 ± 0.82	0.26
Week-4	27	1.96 ± 0.73	<0.001
Week-8	27	0.98 ± 0.65	<0.001
Week-12	26	0.49 ± 0.54	<0.001
Group B: (0.625 CE/2.5 MPA):			
Week-1	34	9.50 ± 0.73	0.93
Week-4	33	3.38 ± 0.66	<0.001
Week-8	31	1.55 ± 0.61	<0.001
Week-12	32	1.16 ± 0.49	<0.001
Group C: (0.45 CE):			
Week-1	32	9.26 ± 0.75	0.89
Week-4	32	5.07 ± 0.67	0.002
Week-8	32	2.85 ± 0.60	<0.001
Week-12	30	2.32 ± 0.50	<0.001
Group D; (0.45 CE/2.5 MPA):			
Week-1	28	9.98 ± 0.81	0.62
Week-4	27	2.45 ± 0.73	<0.001
Week-8	27	1.19 ± 0.65	<0.001
Week-12	26	1.02 ± 0.54	<0.001
Group E: (0.45 CE/1.5 MPA):			
Week-1	29	9.99 ± 0.79	0.61
Week-4	28	3.23 ± 0.72	<0.001
Week-8	27	1.49 ± 0.65	<0.001
Week-12	27	0.94 ± 0.53	<0.001
Group F: (0.3 CE):			
Week-1	30	8.90 ± 0.78	0.65
Week-4	30	4.19 ± 0.70	<0.001
Week-8	29	2.44 ± 0.63	<0.001
Week-12	29	2.01 ± 0.52	<0.001
Group G: (0.3 CE/1.5 MPA):			
Week-1	32	10.60 ± 0.76	0.28
Week-4	32	3.84 ± 0.67	<0.001
Week-8	32	2.41 ± 0.60	<0.001
Week-12	31	1.13 ± 0.50	<0.001
Group H: (Placebo):			
Week-1	28	9.41 ± 0.81	-
Week-4	28	8.09 ± 0.72	-
Week-8	27	7.10 ± 0.65	-
Week-12	25	5.36 ± 0.55	-

*Reviewer's Comments: As seen in the Table, a decrease over time in the **frequency of hot flushes** was observed. These reductions were statistically significant as compared to placebo, at Weeks 4, 8 and 12 in all the active treatment groups. Although not presented here, significant results were observed for the **severity of hot flushes** comparing the active treatment groups to placebo) at Weeks 4, 8 and 12. These results hold after adjustment of alpha level for multiplicity of comparisons.*

Dose response analyses would have been helpful in interpreting the results of this study because of the intentions of each supplemental NDA. One intention was to establish the safety and efficacy of the new low dose of Premarin (0.45 mg) tablets administered alone[ ] [ ] A second intention was to establish the safety and efficacy of[ ]new lower combination doses of CE/MPA (.45 mg CE/1.5 mg MPA [ ]

Summary of Results:
All active treatment groups in the EE population had a significantly lower mean daily number and severity of hot flushes than the placebo group. These statistically significant differences ($p \leq 0.05$) were seen at Week 4, 8 and 12 of therapy. Differences between treatment groups were similar for each of 3 age categories (<50, 50-59, ≥60 years).

Safety Related Discontinuations:
Adverse events led to withdrawal from the study of a total of 266/2673=10% patients. They were as follows:
Groups: A: 73 (21%), B: 31 (9%), C: 36 (11%), D: 24 (7%), E: 30 (9%), F: 21 (6%), G: 30 (9%), H: 21 (6%).

Conclusion:
The vasomotor endpoints were the average daily frequency and severity of MSVS. There was a significantly lower number and severity of hot flushes in all active treatment groups in the EE population compared with the placebo group. These differences were significant at Weeks 4, 8 and 12.

An ITT analysis of the EE subgroup was not done. However, because data were missing for at most 2 subjects in each treatment group, it is highly unlikely the results reported in this review would change with an ITT analysis.

Differences between treatment groups were similar for each of the 3 age groups (<50, 50-59, ≥60).

Reviewer's Comments: Each dose of CE and each combination of CE/MPA appear to be superior to placebo in reduction of the number and severity of moderate to severe hot flushes in healthy postmenopausal women with intact uterus.

Shahla S. Farr, M.S.
Mathematical Statistician, Biometrics II

Concur: Lisa Kammerman, Ph.D.
Team Leader, Biometrics II

Edward Nevius, Ph.D.
Division Director, Biometrics II

cc:
HFD-580/Dr. Van Der Vlugt
HFD-580/Dr. Slaughter
HFD-580/Dr. Allen
HFD-580/Ms. Moore
HFD-715/Ms. Farr
HFD-715/Dr. Kammerman
HFD-715/Dr. Nevius
HFD-715/Dr. Welch
HFD-700/Dr. Anello

This review contains 6 pages

/s/

Lisa A. Kammerman
3/18/01 06:14:36 PM
BIOMETRICS
I am signing and submitting this review on behalf of Ms. Shahla Farr, who is the author of this review. I concur with her review.

S. Edward Nevius
3/18/01 06:17:09 PM
BIOMETRICS
Concur with review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 04-782/S-115 & S-130

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	**04-782 SE2-115**
Compound:	0.45 mg conjugated estrogens oral tablet
Sponsor:	Wyeth-Ayerst Research
Type of Submission:	Efficacy Supplement
Submission Dates:	04-782 SE2-115, July 31, 2000; SE2-115 BB, October 24, 2000; SC2-115-BB, January 11, 2001; SE2-115-BB, May 9, 2001; SE2-115-BB, May 24, 2001.
Reviewer:	S.W. Johnny Lau, R.Ph., Ph.D.

Synopsis:
NDA 04-782 SE2-115 (IND 21,696) proposes the continuous daily 0.45 mg conjugated estrogens (CE) oral tablet for the treatment of moderate to severe vasomotor symptoms associated with menopause as well as the treatment of vulvar and vaginal atrophy was submitted on July 31, 2000.

Sponsor conducted a clinical safety and efficacy study (0713D2-309-US; Health and Osteoporosis, Progestin and Estrogen (HOPE) study, which had the 0.45 mg CE alone treatment and placebo groups) to support NDA 04-782 SE2-115. Sponsor conducted a relative bioavailability study (0713D2-119-US) to support the Human Pharmacokinetics and Bioavailability section of NDA 04-782 SE2-115. Study 0713D2-119-US was a randomized, single-dose, 4-period/treatment, crossover study, which concerns 2 x 0.625 mg CE/2.5 mg MPA, 2 x 0.45 mg CE/2.5 mg MPA, 2 x 0.45 mg CE/1.5 mg MPA, and 2 x 0.45 mg CE alone oral tablets.

The CE formulations tested in the clinical studies 0713D2-309-US and 0713D2-119-US are identical to the to-be-marketed formulations in terms of scale of manufacture and composition except the color coat, which was white in the clinical formulations. This color change between the clinical batch and to-be-marketed batch was justified via in vitro dissolution data.

Sponsor's proposed in vitro dissolution method and specifications for the 0.45 mg CE tablet are acceptable. Briefly,

Sponsor's proposed in vitro dissolution method for CE (the USP 24 method):	
Apparatus	USP Apparatus 2
In vitro release medium	water
Volume of release medium	900 mL
Medium temperature	37 ± 0.5°C
Stirring speed	50 rpm

CE in vitro dissolution specifications:	
	Proposed, % estrone sulfate released
2 hours	between 19% and 49%
5 hours	between 66% and 96%
8 hours	not less than 80%

Recommendations:
The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 04-782 SE2-115 dated July 31, 2000. OCPB finds that the submitted information supports the Human Pharmacokinetics and Bioavailability section of NDA 04-782 SE2-115. However, the Clinical Pharmacology labeling comments in Review Question 7 should be communicated to the sponsor.

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

An Optional Intra-Division Clinical Pharmacology and Biopharmaceutics Briefing for NDA 04-782 SE2-115 was conducted on July 17, 2001; participants included D. Moore, D. Lin, H. Malinowski, J. Hunt, A. Parekh, S. Al-Habet, and J. Lau.

FT signed by Ameeta Parekh, Ph.D., Team Leader 7/ /01

cc: NDA 04-782, HFD-870 (H. Malinowski, A. Parekh, J. Lau), HFD-580 (T. van der Vlugt, D. Moore), HFD-820 (D. Lin), CDR (B. Murphy for Drugs)

Background:
Sponsor also submitted NDA 20-527 SLR-017 for the 0.45 mg CE/1.5 mg MPA [ ] [ ] oral tablets on June 15, 2000 for the same indications. [ ] [ ]. PREMARIN® is available as 0.3, 0.625, 0.9, 1.25, and 2.5 mg CE alone oral tablets and is derived from pregnant mares' urine, which contains more than 10 estrogens, including the sodium sulfate conjugates of estrone, equilin, 17α-dihydroequilin, 17β-dihydroequilin, 17α-estradiol, 17β-estradiol, equilenin, 17α-dihydroequilenin, 17β-dihydroequilenin, and $\Delta^{8,9}$-dehydroestrone. Other background material has been covered in the synopsis section above. General CE clinical pharmacology information is in the PREMARIN® labeling. Synopsis for Study 0713D2-119-US is in Attachment 1.

The following questions, based on the content of NDA 04-782 SE2-115, guided this review.

1. What study results are submitted to support the Human Pharmacokinetics (PK) and Bioavailability (BA) section of NDA 04-782 SE2-115?

	Study	Review Question
Bioanalytical assay	-	2
PK of 0.45 mg CE tablet	0713D2-119-US	3
Multiple dose	-	4
Formulation	-	5
In vitro dissolution	-	6
Proposed labeling	-	7

2. What were the bioanalytical methods for CE used in NDA 04-782 SE2-115?
Because of low doses, 2 tablets of each formulation were administered to provide plasma drug concentrations that could be more accurately measured.

Unconjugated and total estrone (baseline adjusted and unadjusted), equilin, 17β-estradiol (baseline adjusted and unadjusted), 17β-dihydroequilin, $\Delta^{8,9}$-dehydroestrone, and 17β-$\Delta^{8,9}$-dehydroestradiol in plasma were determined via gas chromatography/tandem mass spectrometry. Total (unconjugated and conjugated) estrone, equilin, $\Delta^{8,9}$-dehydroestrone, 17β-estradiol, 17β-dihydroequilin and 17β-$\Delta^{8,9}$-dehydro-estradiol concentrations in plasma were determined via the same procedure after [ ] Control samples were also utilized to confirm that the [ ] of the conjugated estrogens was complete. The inter-day % CV for CE analytes for the low, mid, and high quality control samples were mostly below 10% (Attachment 2).

Analyte	¶LLOQ, pg/mL
2 mL plasma sample:	
unconjugated estrone, $\Delta^{8,9}$-dehydroestrone, 17β-dihydroequilin, and 17β-$\Delta^{8,9}$-dehydroestradiol	5
Unconjugated equilin	10
Unconjugated 17β-estradiol	2.5
0.4 mL plasma sample:	
Total equilin	50
total estrone, $\Delta^{8,9}$-dehydroestrone, 17β-dihydroequilin, and 17β-$\Delta^{8,9}$-dehydroestradiol	25
Total 17β-estradiol	12.5

¶LLOQ = lower limit of quantitation

See Attachment 2 for bioanalytical assay validations for Study 0713D2-119-US.

Overall, the bioanalytical assay for CE in plasma was acceptable. However, the CE inter-day coefficient table for Study 0713D2-119-US were not consistent between the study report and the bioanalytical report (slight variations in reported numbers; Attachment 2). Sponsor did not summarize and report the intra-day variation for the CE bioanalytical assay.

3. What is the PK of the 0.45 mg CE oral tablets?
Study 0713D2-119-US contained PK information for the 0.45 mg CE tablets in 1 treatment arm. The study consisted of a single dose oral administration of 2 x 0.625 mg CE/2.5 mg MPA tablets (treatment A), 2 x 0.45 mg CE/2.5 mg MPA tablets (treatment B), 2 x 0.45 mg CE/1.5 mg MPA tablets (treatment C), and 2 x 0.45 mg CE tablets (treatment D). See Attachment 3 for CE figure and PK parameters tables for the 0.45 mg CE tablets.

Generally, the PK of CE upon administration of 0.45 mg CE tablets are comparable to the PK of CE upon administration of 0.45 mg CE/1.5 mg MPA tablets. However, the unconjugated 17β-estradiol t_{max} was 17.5 ± 9.8 hours for the 0.45 mg CE tablet (Attachment 3; Table 6.1.2B) and 14.5 ± 7.3 hours for the 0.45 mg CE/1.5 mg MPA tablets (Attachment 3).

4. Do CE accumulate upon multiple dose administration of 0.45 mg CE oral tablets?
Study 0713D2-119-US is single dose in design and did not address the dose accumulation potential upon multiple-dose administration. PREMARIN® 0.3, 0.625, 0.9, 1.25, and 2.5 mg CE alone oral tablets for continuous daily administration were approved for the same indications as that proposed for the 0.45 mg CE oral tablet via this efficacy supplement. No multiple dose CE PK information is in the current PREMARIN® labeling. Sponsor conducted Study 0713D2-309-US in NDA 04-782 E2-115 to assess the safety and efficacy of 0.45 mg CE oral tablet; though no blood was sampled for CE measurements in this study. Lack of multiple dose PK information for 0.45 mg CE oral tablet may not be a critical issue for this efficacy supplement.

5. What are the formulations used in the clinical studies for NDA 04-782 SLR-017?
The CE present in the tablets are identical to that in the marketed Premarin® products. The 0.45 mg CE tablet uses the same formulation technology as the marketed Premarin® products. The CE formulation (0930287B) tested in the clinical studies 0713D2-309-US and 0713D2-119-US is identical to the market formulations in terms of scale of manufacture and composition except the color coat, which is white for the clinical formulation. See Attachment 4 for formulation information.

Sponsor submitted the in vitro dissolution data (as average and range) to substantiate the similarity between the clinical batch and the market batch via SC2-115-BB on January 11, 2001. Therefore, individual in vitro dissolution data were requested and sponsor responded via SC2-115-BB on May 9, 2001. However, sponsor provided grouped individual dissolution data at the 2, 5, and 8 hours sampled times, which do not allow plotting of dissolution profiles for individual tablets nor calculation for f_2 values.

Sponsor resubmitted individual dissolution data via SE2-115-BB on May 24, 2001 (Attachment 4). Sponsor has 2 in vitro dissolution methods for the 0.45 mg CE tablets. Method 3256-178 without [ ] and Method L20744-005 with [ ] Both methods have the same specifications. This

reviewer chose the in vitro dissolution data for 4 clinical batches and 2 market batches that had the largest standard deviations of CE released and were subjected to both dissolution methods. This reviewer then plotted the individual % CE released versus time profiles (Attachment 4). By overlaying the dissolution profiles between the clinical batch over the market batch, the 0.45 mg CE tablets dissolution profiles appear to be similar. The f_2 values between the clinical batch and market batch were also calculated (Attachment 4). The f_2 values were 44.4, 50.3, 50.6, and 63.6. Comparison between clinical batch 1997B0091 and market batch A00D003 (both underwent test 3256-178 without [ ]) resulted in f_2 values of 44.4. However, the clinical batch 1997B0091 that underwent test 3256-178 without [ ] failed the Level 3 dissolution test. Therefore, this f_2 value (44.4; comparison) may not be appropriate. The other 3 f_2 values were above 50. Based on the individual dissolution profiles and f_2 values, the clinically-tested 0.45 mg CE tablets and the to-be-marketed 0.45 mg CE tablets are deemed to be similar.

6. What are the proposed in vitro dissolution method and specifications for the 0.45 mg CE tablets?

Sponsor's proposed in vitro dissolution method for CE (the USP 24 method):	
Apparatus	USP Apparatus 2
In vitro release medium	water
Volume of release medium	900 mL
Medium temperature	37 ± 0.5°C
Stirring speed	50 rpm

CE in vitro dissolution specifications:	
	Proposed, % estrone sulfate released
2 hours	between 19% and 49%
5 hours	between 66% and 96%
8 hours	not less than 80%

Sponsor's proposed in vitro dissolution method and specifications for the 0.45 mg CE tablet are acceptable, which are also identical to the specifications for the 0.3 and 0.625 mg CE tablets of the marketed products.

7. What are sponsor's proposed labeling for products' Clinical pharmacology section?
Future Clinical Pharmacology section for PREMARIN®, PREMPRO™, and PREMPHASE® labeling should be consistent between products. Due to the length of sponsor's proposed labeling, only the clinical pharmacology section will be presented in Attachment 5. Labeling comments follow (unwanted parts are deleted and added parts are underscored):

CLINICAL PHARMACOLOGY

[ ]

4 page(s) of draft labeling has been removed from this portion of the review.

Clinical Pharmacology / Biopharmaceutics Review (7/23/01)

Attachment 1

STUDY TITLE: A SINGLE-DOSE, COMPARATIVE BIOAVAILABILITY STUDY OF PREMARIN AND MEDROXYPROGESTERONE ACETATE (MPA) FROM THREE STRENGTHS OF PREMARIN/MPA COMBINATION TABLETS AND ONE STRENGTH OF A PREMARIN-ONLY TABLET IN HEALTHY, POSTMENOPAUSAL WOMEN: FINAL REPORT (Protocol **0713D2-119-US**, GMR-32506)

INVESTIGATORS: [redacted]

STUDY CENTERS: [redacted]

PUBLICATION (REFERENCE): N/A

STUDY PERIOD :
(DATE OF FIRST ENROLLMENT) 28 Aug 1996
(DATE OF LAST COMPLETION) 20 Jan 1997

CLINICAL PHASE: I

OBJECTIVES: To assess the relative bioavailability of Premarin and MPA contained in three different strengths of Premarin/MPA combination tablets and that of a Premarin-only tablet in healthy, hysterectomized, postmenopausal women.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Healthy women 35 to 65 years old who were . within ± 20% of ideal body weight for their height and frame. The subjects had to be hysterectomized ambulatory women who were either naturally postmenopausal, with little or no ovarian estrogen production, or who had a bilateral oophorectomy (documented by an operative report) because of benign pathologic findings at least 6 months before the study start.

NUMBER OF PATIENTS (PLANNED, ENROLLED, ANALYZED):
32 planned, 35 enrolled, 32 completed, 31 analyzed.

DURATION OF TREATMENT: Each subject participated in the clinical portion of the study for approximately 99 days, which included four 9-day study periods with at least 30-day washout intervals. Each study period consisted of a 2 ½-day (3 night) inpatient stay and 6 outpatient visits. The duration of the study was 5 months.

STUDY DRUG, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: Treatment A: two tablets of Premarin 0.625 mg/MPA 2.5 mg (combination-tablet formulation), batch no. 2TQA. Treatment B: two tablets of Premarin 0.45 mg/MPA 2.5 mg (combination-tablet formulation), batch no. 3TEN. Treatment C: two tablets of Premarin 0.45 mg/MPA 1.5 mg (combination-tablet formulation), batch no. 3TEM. Treatment D: two tablets of Premarin 0.45 mg, batch no. 3TEL.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: None

PHARMACOKINETIC AND STATISTICAL METHODS: Noncompartmental pharmacokinetic methods were used to analyze the plasma concentration data. Statistical comparisons were made by using an analysis of variance (ANOVA) for a four-period crossover design. Pairwise comparisons between treatments were made by using Duncan's Multiple Range Test for p-values ≤ 0.05.

SAFETY ASSESSMENT METHODS: A complete medical, gynecologic, and physical examination, with measurement of vital signs and hematologic, biochemical, renal, hepatic, and urinary laboratory determinations, was done at screening and study completion. During the treatment period, study events and symptoms, as well as vital signs and concomitant medications, were evaluated and recorded in the case report form.

PHARMACOKINETIC RESULTS: The comparative bioavailabilities for Premarin components and MPA were evaluated following administration of two Premarin 0.625-mg/MPA 2.5-mg tablets (treatment A), two Premarin 0.45-mg/MPA 2.5-mg tablets (treatment B), two Premarin 0.45-mg/MPA 1.5-mg tablets (treatment C), and two Premarin 0.45-mg tablets (treatment D). All of the Premarin estrogens with estimable peak concentration (C_{max})and area under the concentration-time curve (AUC) showed significant treatment differences for these parameters. In general, results of the

Duncan's Multiple Range Test indicated that the three 0.45-mg Premarin treatments produced lower estrogen concentrations than the 0.625-mg Premarin treatment. The ratios of mean C_{max} for estrogens observed following treatments B, C, and D to mean C_{max} following treatment A ranged from 56% to 76%; and the ratios of mean AUC ranged from 57% to 84%, which are reasonably close to the theoretical value of 72%.

Significant treatment differences were seen for C_{max} and AUC of MPA, and the Duncan's Multiple Range Test indicated that the 1.5-mg MPA treatment produced lower MPA concentrations than the two 2.5-mg MPA treatments. The ratios of mean C_{max} following treatment C to mean C_{max} following treatments A and B were 53% and 68%, respectively; and the ratios of mean AUC were 62% and 63%, respectively, which are very close to the theoretical value of 60%.

SAFETY RESULTS: There were no serious or unexpected adverse events. All events were treatment emergent; headache was the most common adverse event. Eight (8) headaches were reported by 7 subjects; all but 1 of these were considered to be possibly drug related. One (1) headache (drug-related) was severe. There were isolated increases and decreases from baseline in laboratory values, vital signs, and weight, but none of these were considered clinically important.

CONCLUSION: The two Premarin 0.45-mg/MPA 2.5-mg combination tablets, two Premarin 0.45-mg/MPA 1.5-mg combination tablets, and two Premarin 0.45-mg tablets produced lower estrogen concentrations than the two Premarin 0.625-mg/MPA 2.5-mg combination tablets, in line with the relative doses. The two Premarin 0.45-mg/MPA 1.5-mg combination tablets produced lower MPA concentrations than the two Premarin 0.625-mg/MPA 2.5-mg combination tablets, or the two Premarin 0.45-mg/MPA 2.5-mg combination tablets—approximately 60% of the larger MPA dose. The various dose strengths of Premarin and MPA behave pharmacokinetically in a dose-proportional manner.

DATE OF THE REPORT: 09 Jul 1999

Attachment 2

The CE inter-day coefficient of variation (%CV) and the mean bias for the low, mid, and high quality control samples are summarized below for Study 0713D2-119-US (from *study report*).

TABLE 6.5.2A. INTER-DAY COEFFICIENT OF VARIATION (% CV) AND MEAN BIAS

		-----Unconjugated-----		----------Total---------	
Analyte	QC	% CV	% Bias	% CV	% Bias
Estrone	Low	9.7	6.7	13.3	0.0
	Mid	5.7	-3.1	3.1	-1.1
	High	6.0	-1.4	4.0	0.4
Equilin	Low	6.5	1.3	7.6	-1.0
	Mid	3.4	-3.0	4.1	-2.0
	High	4.8	-1.3	5.5	-1.6
$\Delta^{8,9}$-Dehydroestrone	Low	14.3	-8.0	7.6	-8.7
	Mid	7.6	-3.5	19.1	-6.7
	High	5.2	-5.0	6.4	1.0
17β-Estradiol	Low	11.6	2.9	14.9	-2.7
	Mid	6.6	1.2	3.9	3.4
	High	4.8	1.0	3.9	3.5
17β-Dihydroequilin	Low	8.6	-2.7	4.3	4.0
	Mid	6.1	-3.9	4.2	-3.2
	High	7.9	-2.5	5.5	-1.5
17β-$\Delta^{8,9}$-Dehydroestradiol	Low	11.5	-5.3	7.7	-4.7
	Mid	4.9	-4.9	15.0	-5.5
	High	4.0	-4.0	7.7	-2.0

Study 0713D2-119-US:

Analyte	Standard curve range, pg/mL
Estrone	5 - 1000
Equilin	10 - 1000
$\Delta^{8,9}$-Dehydroestrone	5 - 250
17β-Estradiol	2.5 - 250
17β-Dihydroequilin	5 - 250
17β-$\Delta^{8,9}$-Dehydroestradiol	5 - 250

The CE inter-day coefficient of variation (%CV) and the mean bias for the low, mid, and high quality control samples are summarized below for Study 0713D2-119-US (from *bioanalytical report*) on the next page.

		Unconjugated		Total	
Analyte	QC	% CV	% Bias	% CV	% Bias
Estrone	Low	10.9	0.7	11.0	-0.7
	Mid	6.2	-1.8	7.5	-4.0
	High	7.7	-0.6	6.8	-3.9
Equilin	Low	9.3	-6.7	10.3	-10.3
	Mid	7.3	-8.0	11.0	-11.5
	High	8.7	-7.9	7.6	-10.2
$\Delta^{8,9}$-Dehydroestrone	Low	9.8	-2.7	10.7	-2.7
	Mid	5.3	-5.6	11.6	-6.9
	High	6.5	-6.0	6.1	-8.0
17β-Estradiol	Low	11.7	-5.9	10.9	-9.5
	Mid	6.3	0.4	10.6	-0.4
	High	7.2	2.5	5.4	2.0
17β-Dihydroequilin	Low	8.0	-5.3	10.3	-6.7
	Mid	5.3	-4.1	11.0	-5.3
	High	6.1	-3.5	5.2	-5.0
17β-$\Delta^{8,9}$-Dehydroestradiol	Low	10.1	-0.7	15.8	1.3
	Mid	7.4	-2.8	12.3	-4.5
	High	7.3	-2.5	7.3	-3.0

For the analysis of total estrone, equilin, $\Delta^{8,9}$dehydroestrone, 17β-estradiol, 17β-dihydroequilin, and 17β-$\Delta^{8,9}$-dehydroestradiol, additional control samples (n = 3) containing their sulfates (except for 17β-dihydroequilin, which was not available at the time of analysis) were analyzed along with the samples. These control samples (designated as QA samples) were used to verify that the hydrolysis of the conjugated estrogens was complete. Although 17β-dihydroequilin sulfate was not included in the QA samples, total concentrations of 17β-dihydroequilin are reported since there is no reason to believe that the enzyme would not

(Revised: 06-MAY-1998)

Attachment 3

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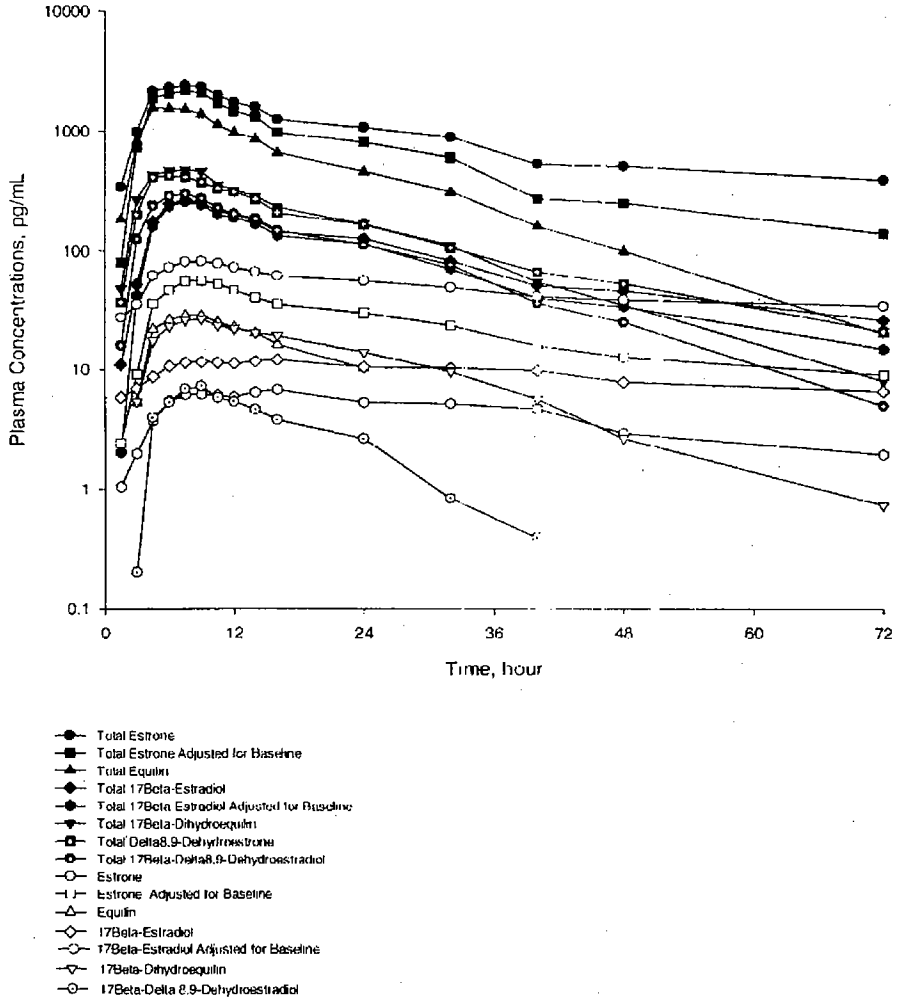
Item 6.1 and Item 8.3.1: Human Pharmacokinetics and Bioavailability Summary

Figure 6.1.2A Mean Estrogen Plasma Concentrations in Postmenopausal Women Receiving 2 x 0.45 mg Conjugated Estrogens



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Item 6.1 and Item 8.3.1: Human Pharmacokinetics and Bioavailability Summary

TABLE 6.1.2B. UNCONJUGATED ESTROGEN PHARMACOKINETIC PARAMETERS (MEAN ± SD) FOLLOWING 2 X 0.45 MG CE ADMINISTRATION

Component	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)
Estrone	91.7 ± 29.0	8.7 ± 2.4	56.4 ± 38.3	6344 ± 3549
Estrone Adjusted for Baseline	65.4 ± 25.9	8.7 ± 2.4	20.3 ± 7.8	1940 ± 779
Equilin	34.8 ± 16.5	7.6 ± 2.5	21.9 ± 24.7	849 ± 513
17β-Estradiol	14.3 ± 5.8	17.3 ± 9.7	47.0 ± 20.4	1152 ± 761
17β-Estradiol adjusted for baseline	9.2 ± 3.7	17.5 ± 9.8	24.6 ± 13.1	401 ± 211
17β-Dihydroequilin	30.5 ± 11.8	8.9 ± 4.1	16.2 ± 4.3	775 ± 264
$\Delta^{8,9}$-Dehydroestrone	6.3 ± 2.1	8.0 ± 2.8	NA[a]	NA
17β-$\Delta^{8,9}$-Dehydroestradiol	9.7 ± 3.3	8.9 ± 1.7	NA	122 ± 90

a: NA = Not available due to low plasma concentrations

Item 6.1 and Item 8.3.1: Human Pharmacokinetics and Bioavailability Summary

TABLE 6.1.2C. TOTAL ESTROGEN PHARMACOKINETIC PARAMETERS (MEAN ± SD) FOLLOWING 2 X 0.45 MG CE ADMINISTRATION

Component	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
Estrone	2.82 ± 1.29	7.1 ± 1.9	27.6 ± 9.6	77.1 ± 25.6
Estrone adjusted for baseline	2.56 ± 1.22	7.1 ± 1.9	14.7 ± 6.2	48.0 ± 17.9
Equilin	1.86 ± 0.96	5.9 ± 1.9	11.8 ± 3.8	29.2 ± 15.9
17β-Estradiol	0.37 ± 0.21	10.4 ± 6.6	22.9 ± 12.7	7.3 ± 2.0
17β-Estradiol adjusted for baseline	0.35 ± 0.21	10.4 ± 6.6	18.4 ± 11.1	6.0 ± 2.4
17β-Dihydroequilin	0.58 ± 0.28	6.6 ± 2.2	12.4 ± 4.6	9.8 ± 4.5
$\Delta^{8,9}$-Dehydroestrone	0.48 ± 0.18	6.3 ± 1.8	18.3 ± 5.4	10.0 ± 3.5
17β-$\Delta^{8,9}$-Dehydroestradiol	0.34 ± 0.21	7.1 ± 2.0	13.1 ± 3.8	6.1 ± 3.5

Attachment 4

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Item 6.1 and Item 8.3.1: Human Pharmacokinetics and Bioavailability Summary

6.1.3 Drug Formulations

The 0.45 mg CE dosage form uses the same formulation technology as the currently marketed Premarin products. The CE/MPA dosage forms consist of a core tablet containing CE, which is [ ]. MPA, a second active component, is then [ ] [ ]. The clinical formulations (CE and CE/MPA) used in the clinical pharmacology study (protocol 713D2-119-US) are identical to the marketed formulations in terms of scale of manufacture and composition except for the color coat, which is white in the case of the clinical formulation. The referenced clinical batches were manufactured at Wyeth-Ayerst Laboratories, Rouses Point, New York.

The CE present in the tablets is identical to the drug substance used in oral Premarin marketed products. The source of the [ ] and the conjugated estrogens [ ] are also the same as for the currently marketed Premarin tablets.

[ ]

Table 6.1.3A lists the formulations for the CE and CE/MPA tablets used in the referenced clinical studies.

TABLE 6.1.3A FORMULATIONS USED IN CLINICAL STUDIES

	Study	
Component (mg)	119-US	309-US
CE 0.3		0930329B
CE 0.45	0930287B	0930287B
CE 0.625		0929535B
CE 0.3/MPA 1.5		0930328B
CE 0.45/MPA 1.5	0930288B	0930288B
CE 0.45/MPA 2.5	0930289B	0930289B
CE 0.625/MPA 2.5	0930230B	0930230B

Item 6.1 and Item 8.3.1: Human Pharmacokinetics and Bioavailability Summary

Table 6.1.3B presents specific batch information for the tablets used in the pharmacokinetic and clinical efficacy studies.

TABLE 6.1.3B TABLETS USED IN CLINICAL STUDIES

Component (mg)	Formulation Number	Batch Number	Study	Month of Manufacture
CE 0.3	0930329B	3THP	309-US	3/94
		1997B0092	309-US	7/97
CE 0.45	0930287B	3TEL	119-US	11/93
		1997B00091	309-US	7/97
CE 0.625	0929535B	3TFQ	309-US	5/93
		9610332	309-US	6/96
CE 0.3/MPA 1.5	0930328B	1997B0093	309-US	7/97
CE 0.45/MPA 1.5	0930288B	3TEM	119-US	11/93
			309-US	
		1997B0089	309-US	7/97
CE 0.45/MPA 2.5	0930289B	3TEN	119-US	11/93
		1997B0090	309-US	7/97
CE 0.625/MPA 2.5	0930230B	2TQA	119-US	7/93
		2TPW	309-US	6/93
		2TPT	309-US	5/93
		9610328	309-US	6/96

Formulation details for the batches used in the current clinical protocols, including 0.3 mg, 0.45 mg, and 0.625 mg CE cores and subsequent [redacted] loads leading to the 0.3 mg/1.5 mg, 0.45 mg/1.5 mg, 0.45 mg/2.5 mg, and 0.625 mg/2.5 mg CE/MPA are presented in Table 6.1.3C.

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TABLE 6.1.3C COMPOSITION OF CLINICAL TRIAL FORMULATIONS USED IN PIVOTAL CLINICAL STUDIES

	Amount per Tablet (mg)						
	0.3 mg	0.45 mg	0.625 mg	0.3mg/ 1.5 mg	0.45 mg/ 1.5 mg	0.45 mg/ 2.5 mg	0.625 mg/ 2.5 mg
	Formulation						
Ingredients	0930329B	0930287B	0929535B	0930328B	0930288B	0930289B	0930230B
[redacted] Tablet							
Conjugated Estrogens (CE) [redacted]	[redacted]						
[redacted]							
Lactose [redacted]							
Methylcellulose [redacted]							
Magnesium stearate							
[redacted]							
[redacted]							
Polyethylene glycol [redacted]							
Glyceryl monooleate							
[redacted]							
Pharmaceutical glaze[a]							
Calcium sulfate [redacted]							

TABLE 6.1.3C COMPOSITION OF CLINICAL TRIAL FORMULATIONS USED IN PIVOTAL CLINICAL STUDIES

	Amount per Tablet (mg)						
	0.3 mg	0.45 mg	0.625 mg	0.3mg/ 1.5 mg	0.45 mg/ 1.5 mg	0.45 mg/ 2.5 mg	0.625 mg/ 2.5 mg
	Formulation						
Ingredients	0930329B	0930287B	0929535B	0930328B	0930288B	0930289B	0930230B
[redacted]							
[redacted] cellulose							
Sucrose							
Titanium dioxide							
[redacted]							
MPA [redacted]							
Medroxyprogesterone acetate[b]							
Povidone							
[redacted] cellulose							
Sucrose							
[redacted]							

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Item 6.1 and Item 8.3.1: Human Pharmacokinetics and Bioavailability Summary

TABLE 6.1.3C COMPOSITION OF CLINICAL TRIAL FORMULATIONS USED IN PIVOTAL CLINICAL STUDIES

	Amount per Tablet (mg)						
	0.3 mg	0.45 mg	0.625 mg	0.3mg/ 1.5 mg	0.45 mg/ 1.5 mg	0.45 mg/ 2.5 mg	0.625 mg/ 2.5 mg
	Formulation						
Ingredients	0930329B	0930287B	0929535B	0930328B	0930288B	0930289B	0930230B
[redacted]							
Sucrose							
Titanium dioxide							
[redacted]							
Carnauba wax							
[redacted]							
Composition Notes:							

Premarin 0.45 mg Tablets

Table 1
Dissolution Data Generated Using The USP 24 Method (3256-178) and The USP 24 Method With [ ] (L20744-005)
for Registration Lots of Premarin 0.45 mg Tablets Submitted in the sNDA
Stored in [ ] Bottles at 25°C/60% RH for 9 months
Specifications: 2 hours = 19 – 49%; 5 hours = 66 – 96%; 8 hours = Not less than 80%
Units: % Released

A00D001	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: 3256-178 without [ ]										
2 hours	[ ]						31	5.26	[ ]	Level 1
5 hours							80	6.75		
8 hours							96	4.33		

A00D001	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Tablet 7	Tablet 8	Tablet 9	Tablet 10	Tablet 11	Tablet 12	Mean	Std. Dev.	Range	Accept. Criteria
Method: L20744-005 with [ ]																
2 hours	[ ]												31	8.02	[ ]	Level 2
5 hours													79	5.02		
8 hours													96	2.23		

A00D002	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: 3256-178 without [ ]										
2 hours	[ ]						37	9.55	[ ]	Level 1
5 hours							83	7.08		
8 hours							97	3.58		

Premarin 0.45 mg Tablets

Table 1 (cont.)
Dissolution Data Generated Using The USP 24 Method (3256-178) and The USP 24 Method With [ ] (L20744-005)
for Registration Lots of Premarin 0.45 mg Tablets Submitted in the sNDA
Stored in [ ] Bottles at 25°C/60% RH for 9 months
Specifications: 2 hours = 19 – 49%; 5 hours = 66 – 96%; 8 hours = Not less than 80%
Units: % Released

A00D002	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: L20744-005 with [ ]										
2 hours	[					]	30	7.09	[ ]	Level 1
5 hours							78	6.13		
8 hours							96	3.54		

A00D003	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Tablet 7	Tablet 8	Tablet 9	Tablet 10	Tablet 11	Tablet 12	Mean	Std. Dev.	Range	Accept. Criteria
Method: 3256-178 without [ ]																
2 hours	[											]	38	11.49	[ ]	Level 2
5 hours													87	6.74		
8 hours													100	2.62		

A00D003	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: L20744-005 with [ ]										
2 hours	[					]	35	7.75	[ ]	Level 1
5 hours							84	4.13		
8 hours							99	2.33		

Premarin 0.45 mg Tablets

Table II

Dissolution Data Generated Using The USP 24 Method (3256-178) and The USP 24 Method With [ ] (L20744-005)
for Registration Lots of Premarin 0.45 mg Tablets Submitted in the sNDA
Stored in [ ] Bottles at 25°C/60% RH for 12 months
Specifications: 2 hours = 19 – 49% ; 5 hours = 66 – 96% ; 8 hours = Not less than 80%
Units: % Released

A00D001	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: 3256-178 without [ ]										
2 hours	[					]	34	7.13	[ ]	Level 1
5 hours							84	4.52		
8 hours							98	2.49		

A00D001	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: 3256-178 with [ ]										
2 hours	[					]	[illegible]	[illegible]	[ ]	Level 1
5 hours							82	1.84		
8 hours							99	1.17		

A00D002	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: 3256-178 without [ ]										
2 hours	[					]	36	7.34	[ ]	Level 1
5 hours							83	3.73		
8 hours							99	2.15		

Premarin 0.45 mg Tablets

Table II (cont.)

Dissolution Data Generated Using The USP 24 Method (3256-178) and The USP 24 Method With [ ] (L20744-005)
for Registration Lots of Premarin 0.45 mg Tablets Submitted in the sNDA
Stored in [ ] Bottles at 25°C/60% RH for 12 months
Specifications: 2 hours = 19 – 49%; 5 hours = 66 – 96%; 8 hours = Not less than 80%
Units: % Released

A00D002	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: L20744-005 with [ ]										
2 hours	[					]	33	6.26	[ ]	Level 1
5 hours							80	5.10		
8 hours							97	3.43		

A00D003	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: 3256-178 without [ ]										
2 hours										
5 hours										
8 hours	..	..								

A00D003	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: L20744-005 with [ ]										
2 hours	[					]	35	6.48	[ ]	Level 1
5 hours							83	4.25		
8 hours							98	3.00		

.. = Testing not scheduled

Premarin 0.45 mg Tablets

Table III

Dissolution Data Generated Using The USP 24 Method (3256-178) and The USP 24 Method With [ ] (1.20744-005)
for Registration Lots of Premarin 0.45 mg Tablets Submitted in the sNDA
Stored in PVC Blisters at 25°C/60% RH for 9 months
Specifications: 2 hours = 19 – 49%; 5 hours = 66 – 96%; 8 hours = Not less than 80%
Units: % Released

A00D001	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: 3256-178 without [ ]										
2 hours	[					]	31	6.75	[ ]	Level 1
5 hours							83	6.71		
8 hours							97	3.53		

A00D001	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method 1.20744-005 with [ ]										
2 hours	[					]	29	3.95	[ ]	Level 1
5 hours							79	2.06		
8 hours							96	1.75		

A00D002	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: 3256-178 without [ ]										
2 hours	[					]	30	6.10	[ ]	Level 1
5 hours							80	6.72		
8 hours							96	3.56		

Premarin 0.45 mg Tablets

Table III (cont.)

Dissolution Data Generated Using The USP 24 Method (3256-178) and The USP 24 Method With [ ] (L20744-005)
for Registration Lots of Premarin 0.45 mg Tablets Submitted in the sNDA
Stored in PVC Blisters at 25°C/60% RH for 9 months
Specifications: 2 hours = 19 – 49%; 5 hours = 66 – 96%; 8 hours = Not less than 80%
Units: % Released

A001D002	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Tablet 7	Tablet 8	Tablet 9	Tablet 10	Tablet 11	Tablet 12	Mean	Std. Dev.	Range	Accept. Criteria
Method: L20744-005 with [ ]																
2 hours	[											]	35	9.37	[	Level 2
5 hours													81	6.57	]	
8 hours													96	2.75		

A001D003	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Tablet 7	Tablet 8	Tablet 9	Tablet 10	Tablet 11	Tablet 12
Method 3256-178 without [ ]												
2 hours	[											]
5 hours												
8 hours												

	Tablet 13	Tablet 14	Tablet 15	Tablet 16	Tablet 17	Tablet 18	Tablet 19	Tablet 20	Tablet 21	Tablet 22	Tablet 23	Tablet 24	Mean	Std. Dev.	Range	Accept. Criteria
2 hours	[											]	37	11.51	[	Level 3
5 hours													87	7.93	]	
8 hours													100	3.11		

Premarin 0.45 mg Tablets

Table III (cont.)
Dissolution Data Generated Using The USP 24 Method (3256-178) and The USP 24 Method With [ ] (L20744-005)
for Registration Lots of Premarin 0.45 mg Tablets Submitted in the sNDA
Stored in PVC Blisters at 25°C/60% RH for 9 months
Specifications: 2 hours = 19 – 49%; 5 hours = 66 – 96%; 8 hours = Not less than 80%
Units: % Released

A00D003	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: L20744-005 with [ ]										
2 hours	[ ]						36	4.22	[ ]	Level 1
5 hours							82	2.97		
8 hours							98	1.86		

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Premarin 0.45 mg Tablets

Table IV
Dissolution Data Generated Using The USP 24 Method (3256-178) and The USP 24 Method With [ ] (L20744-005)
for Registration Lots of Premarin 0.45 mg Tablets Submitted in the sNDA
Stored in PVC Blisters at 25°C/60% RH for 12 months
Specifications: 2 hours = 19 – 49%; 5 hours = 66 – 96%; 8 hours = Not less than 80%
Units: % Released

A00D001	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: 3256-178 without [ ]										
2 hours	--	--	--	--	--	--	--	--	--	--
5 hours	--	--	--	--	--	--	--	--	--	
8 hours	--	--	--	--	--	--	--	--	--	

A00D001	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: L20744-005 with [ ]										
2 hours	[					]	35	8.67	[ ]	Level 1
5 hours							82	5.24		
8 hours							97	2.37		

A00D002	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: 3256-178 without [ ]										
2 hours	--	--	--	--	--	--	--	--	--	--
5 hours	--	--	--	--	--	--	--	--	--	
8 hours	--	--	--	--	--	--	--	--	--	

-- = Testing not scheduled.

Premarin 0.45 mg Tablets

Table IV (cont.)

Dissolution Data Generated Using The USP 24 Method (3256-178) and The USP 24 Method With [redacted] (L20744-005)
for Registration Lots of Premarin 0.45 mg Tablets Submitted in the sNDA
Stored in PVC Blisters at 25°C/60% RH for 12 months
Specifications: 2 hours = 19 – 49%; 5 hours = 66 – 96%; 8 hours = Not less than 80%
Units: % Released

A001D002	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: L20744-005 with [redacted]										
2 hours	[redacted]						36	8.52	[redacted]	Level 1
5 hours							81	5.85		
8 hours							97	2.32		

A001D003	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: 3256-178 without [redacted]										
2 hours	--	--	--	--	--	--	--	--	--	--
5 hours	--	--	--	--	--	--	--	--	--	--
8 hours	--	--	--	--	--	--	--	--	--	--

A00D003	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: L20744-005 with [redacted]										
2 hours	[redacted]						33	7.24	[redacted]	Level 1
5 hours							80	5.22		
8 hours							95	3.09		

-- Testing not scheduled.

Premarin 0.45 mg Tablets

Table V

Dissolution Data Generated Using The USP 24 Method (3256-178) and The USP 24 Method With [ ] (1.20744-005) for Clinical Lots of Premarin 0.45 mg Tablets Submitted in the sNDA

Stored [ ]

Specifications: 2 hours = 19 – 49%; 5 hours = 66 – 96%; 8 hours = Not less than 80%

Units: % Released

Clinical Batch[a]

3TEL	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Tablet 7	Tablet 8	Tablet 9	Tablet 10	Tablet 11	Tablet 12	Mean	Std. Dev.	Range	Accept. Criteria
Method: 3256-178 without [ ]																
2 hours	[											]	22	3.78	[ ]	Level 2
5 hours													82	5.19		
8 hours													97	3.70		

3TEL	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Tablet 7	Tablet 8	Tablet 9	Tablet 10	Tablet 11	Tablet 12	Mean	Std Dev.	Range	Accept Criteria
Method: 1.20744-005 with [ ]																
2 hours	[											]	22	3.68	[ ]	Level 2
5 hours													80	3.18		
8 hours													97	3.61		

1997B0091	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	Std. Dev.	Range	Acceptance Criteria
Method: 3256-178 without [ ]										
2 hours	[					]	58	12.30	[ ]	See Below[b]
5 hours							97	3.72		
8 hours							100	0.83		

a: Batch 3TEL was manufactured during 11/93 and batch 1997B0091 was manufactured during 7/97. The dissolution test results reported were generated during November 2000 by both methods (3256-178 and 1.20744-005).

b: Sample results do not meet USP <724> Level 3 acceptance criteria.

Premarin 0.45 mg Tablets

Table V (cont.)

Dissolution Data Generated Using The USP 24 Method (3256-178) and The USP 24 Method With [ ] (L20744-005)
for Clinical Lots of Premarin 0.45 mg Tablets Submitted in the sNDA

Stored in [ ]

Specifications: 2 hours = 19 – 49%; 5 hours = 66 – 96%; 8 hours = Not less than 80%

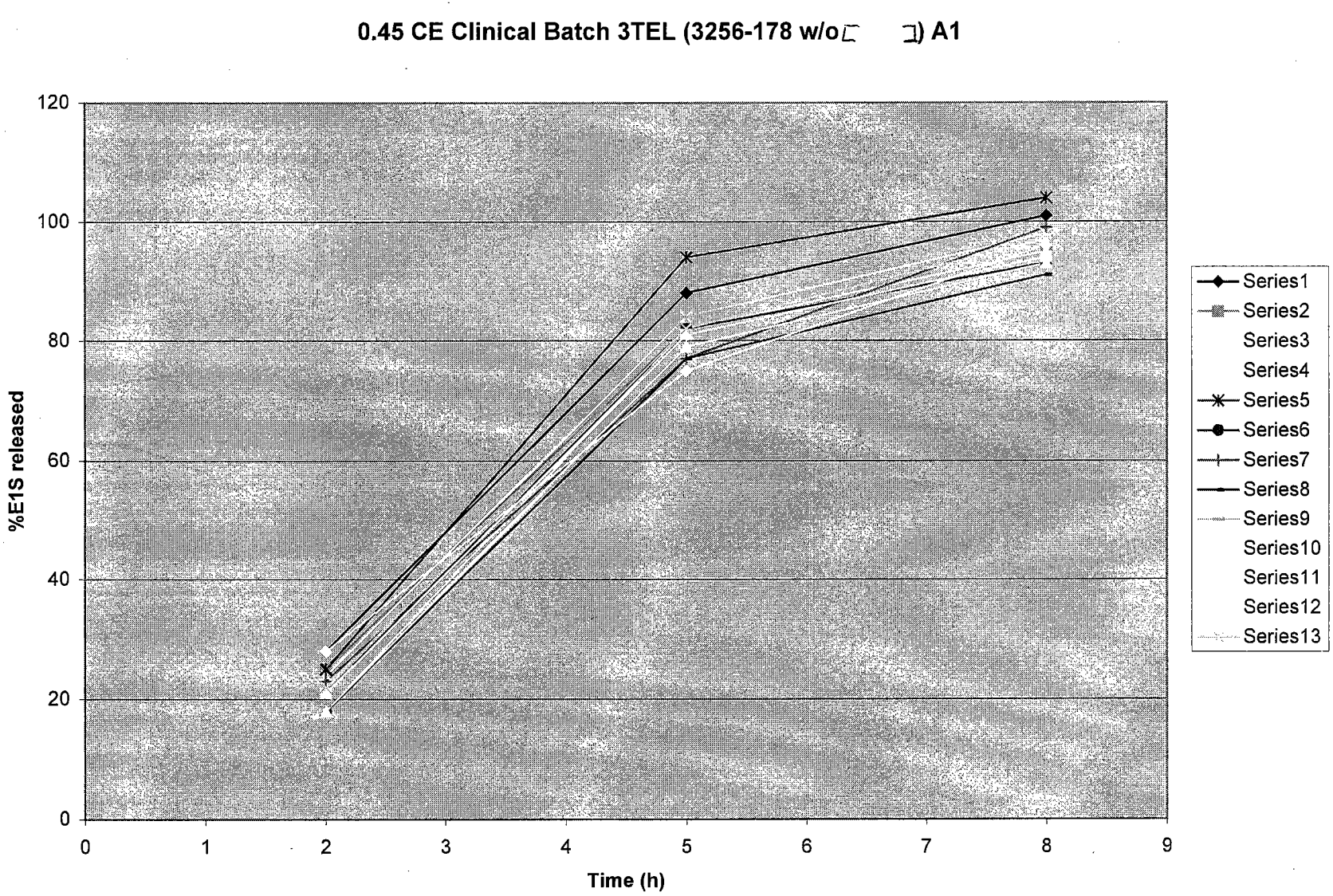
Units: % Released

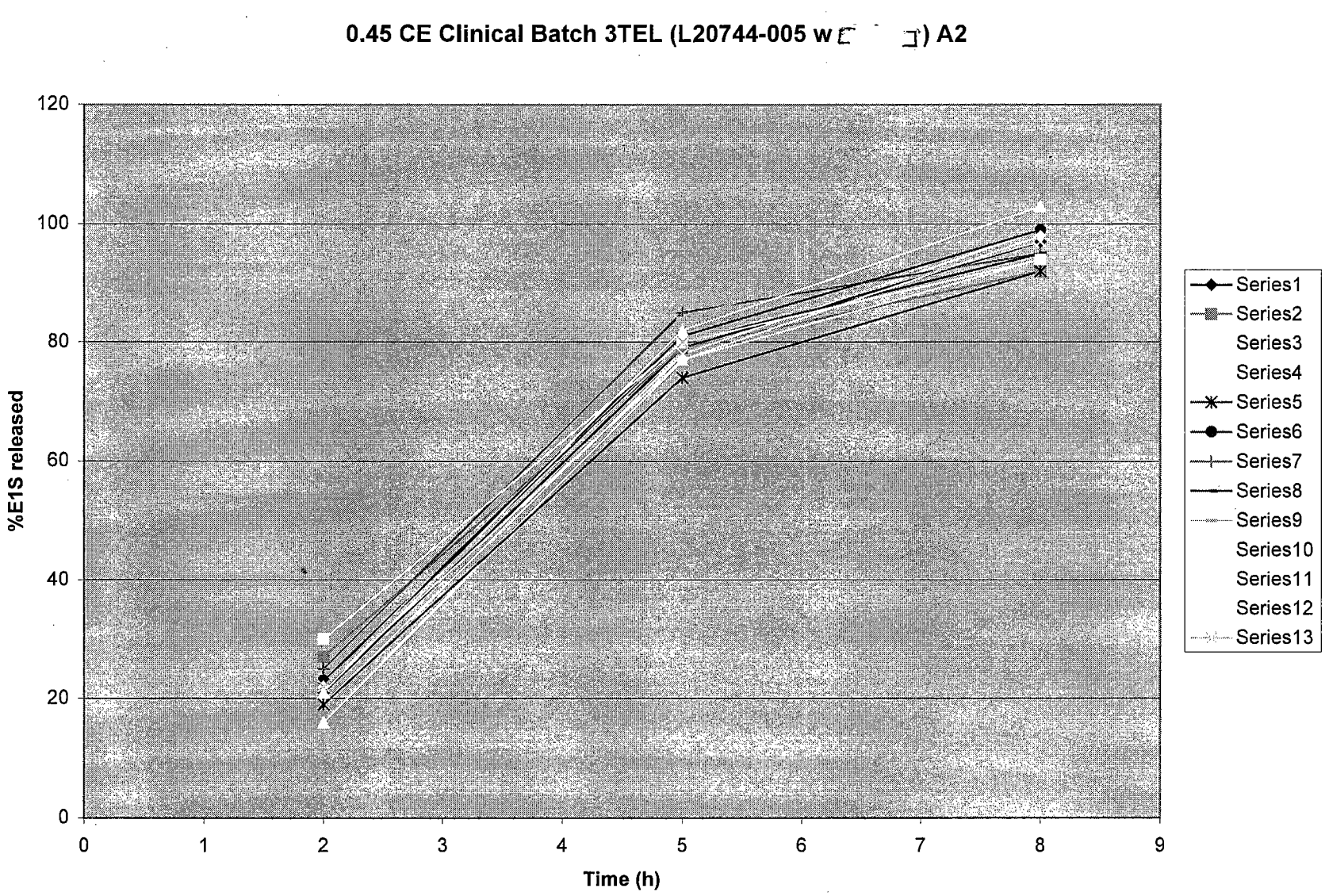
Clinical Batch[a]

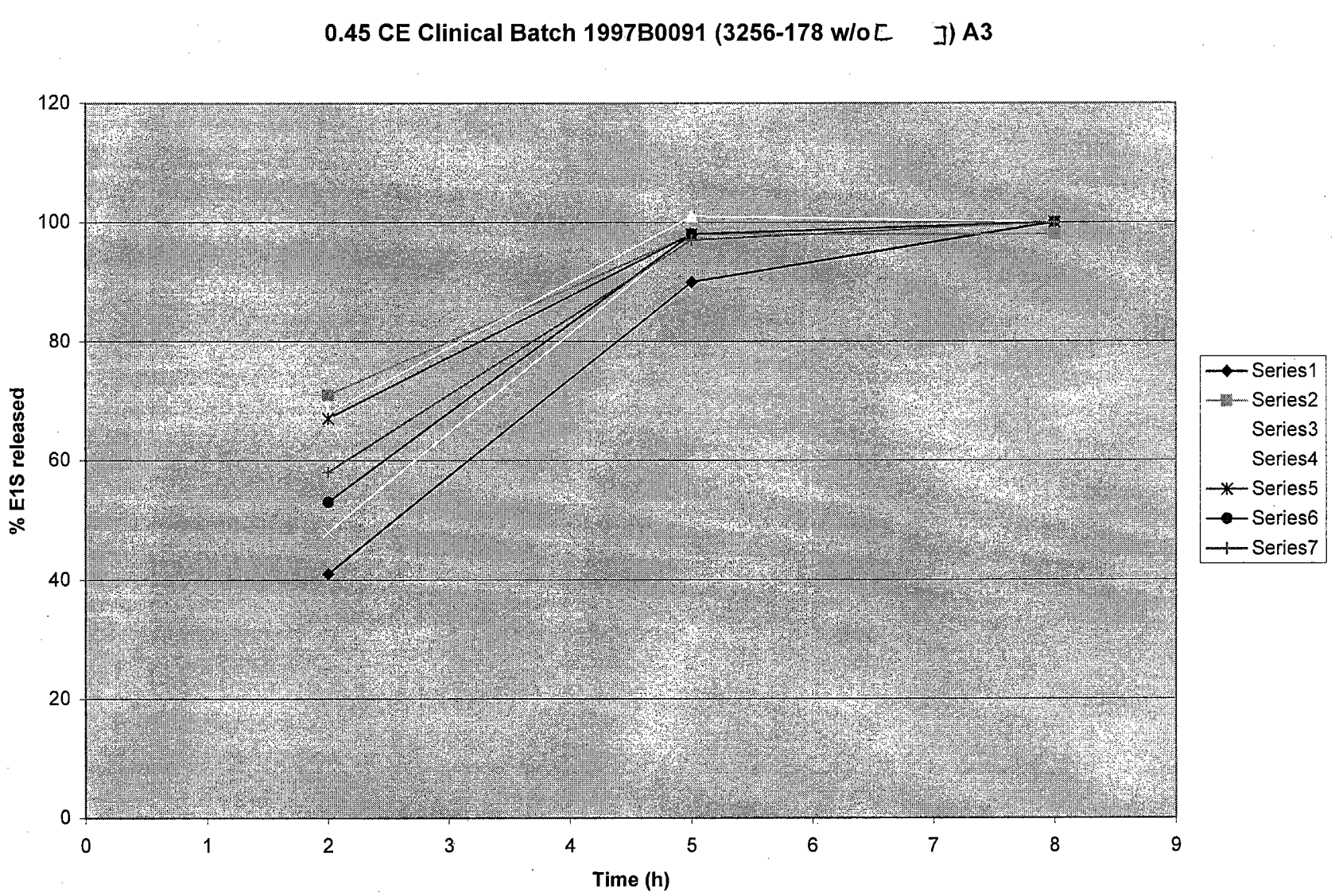
1997B0091	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Tablet 7	Tablet 8	Tablet 9	Tablet 10	Tablet 11	Tablet 12
Method: L20744-005 with [ ]												
2 hours	[											]
5 hours												
8 hours												

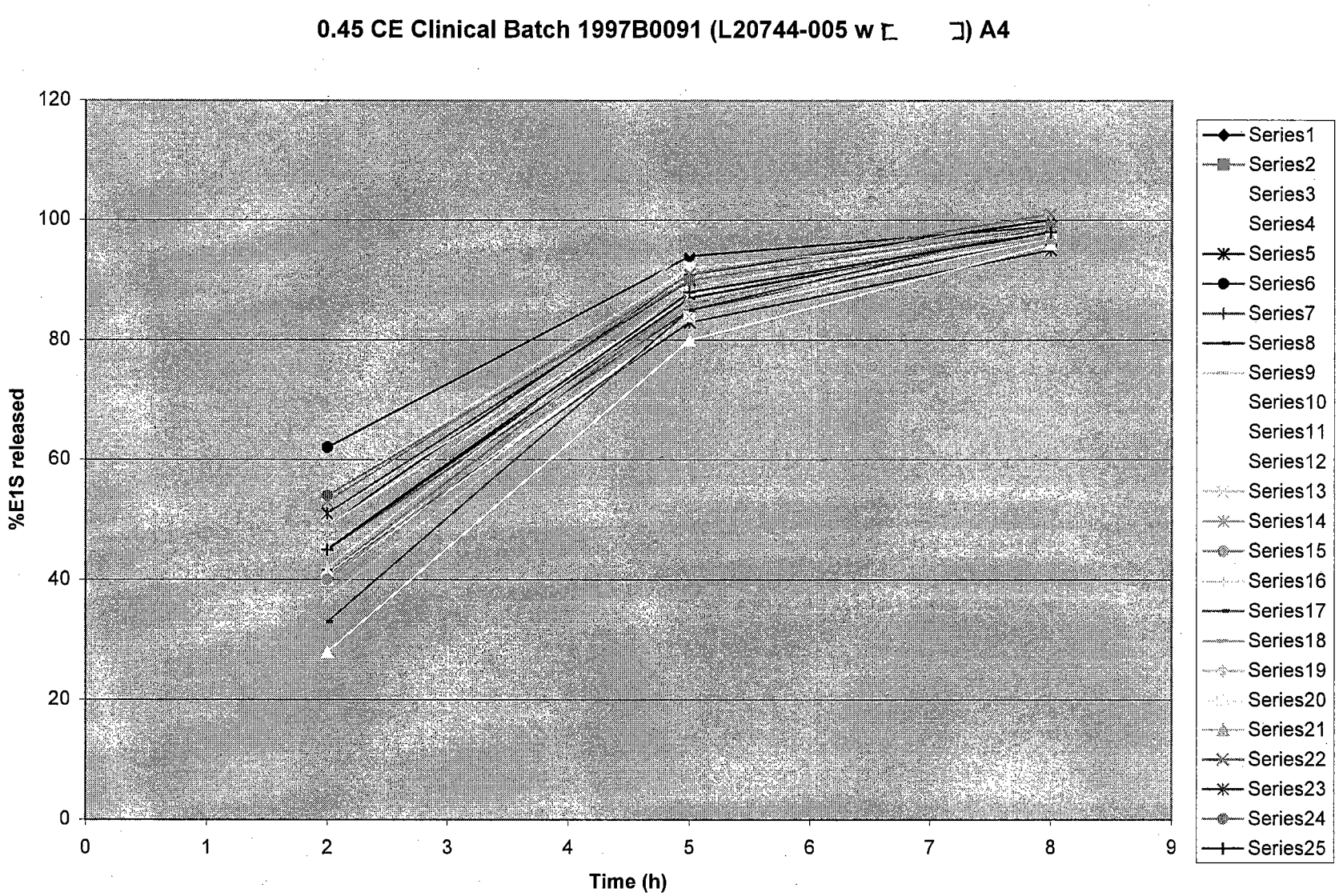
	Tablet 13	Tablet 14	Tablet 15	Tablet 16	Tablet 17	Tablet 18	Tablet 19	Tablet 20	Tablet 21	Tablet 22	Tablet 23	Tablet 24	Mean	Std. Dev.	Range	Accept. Criteria
2 hours	[											]	45	7.17	[ ]	
5 hours													88	3.71		Level 3
8 hours													98	1.60		

a: Batch 3TEL was manufactured during 11/93 and batch 1997B0091 was manufactured during 7/97. The dissolution test results reported were generated during November 2000 by both methods (3256-178 and L20744-005).


0.45 CE Clinical Batch 3TEL (3256-178 w/o) A1
%E1S released
Time (h)
0
20
40
60
80
100
120
0
1
2
3
4
5
6
7
8
9
Series1
Series2
Series3
Series4
Series5
Series6
Series7
Series8
Series9
Series10
Series11
Series12
Series13


0.45 CE Clinical Batch 3TEL (L20744-005 w [illegible]) A2
%E1S released
Time (h)
0
20
40
60
80
100
120
0
1
2
3
4
5
6
7
8
9
Series1
Series2
Series3
Series4
Series5
Series6
Series7
Series8
Series9
Series10
Series11
Series12
Series13


0.45 CE Clinical Batch 1997B0091 (3256-178 w/o) A3
120
100
80
60
40
20
0
% E1S released
0
1
2
3
4
5
6
7
8
9
Time (h)
Series1
Series2
Series3
Series4
Series5
Series6
Series7


0.45 CE Clinical Batch 1997B0091 (L20744-005 w ㄷ ㄱ) A4
%E1S released
Time (h)
0
20
40
60
80
100
120
0
1
2
3
4
5
6
7
8
9
Series1
Series2
Series3
Series4
Series5
Series6
Series7
Series8
Series9
Series10
Series11
Series12
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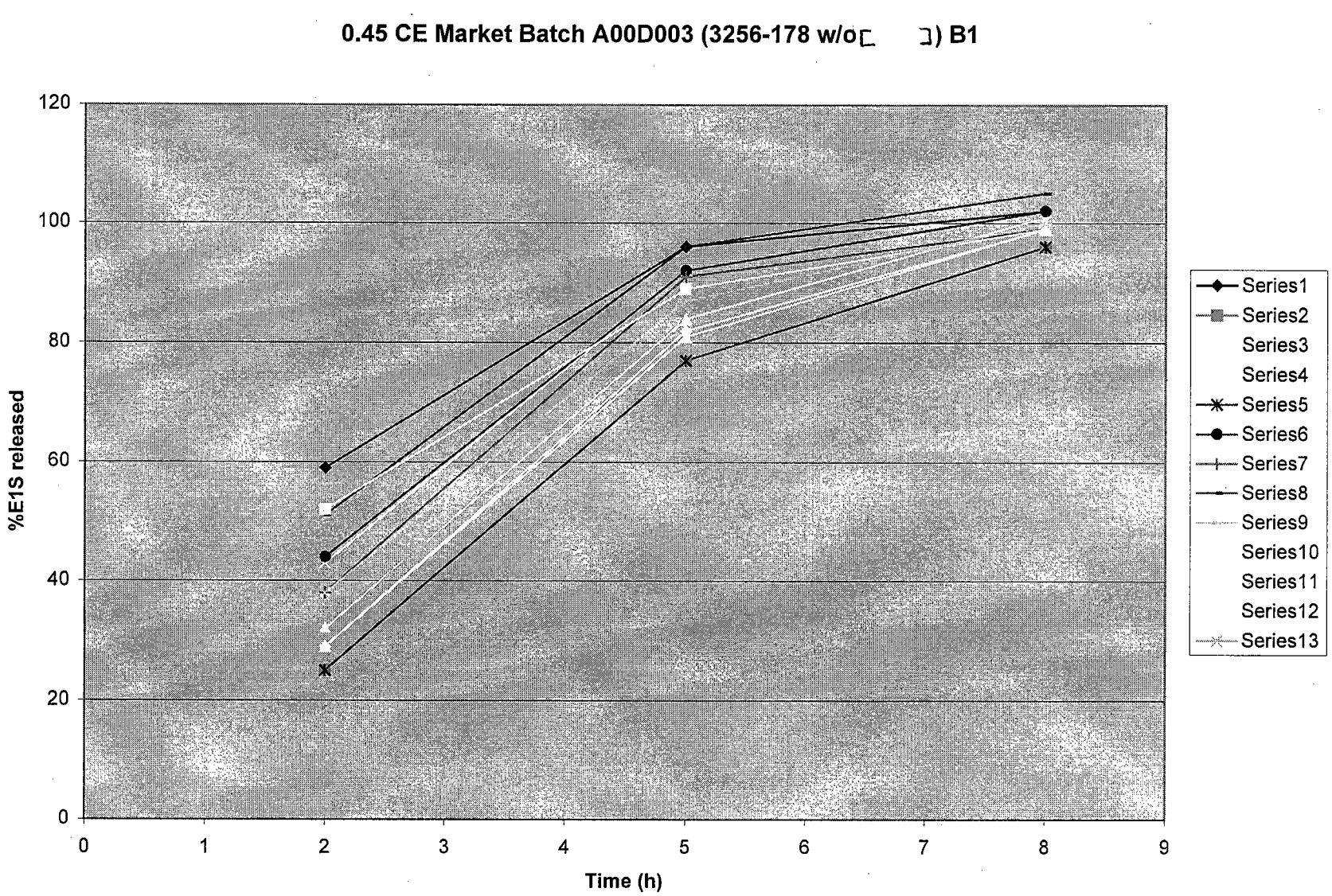
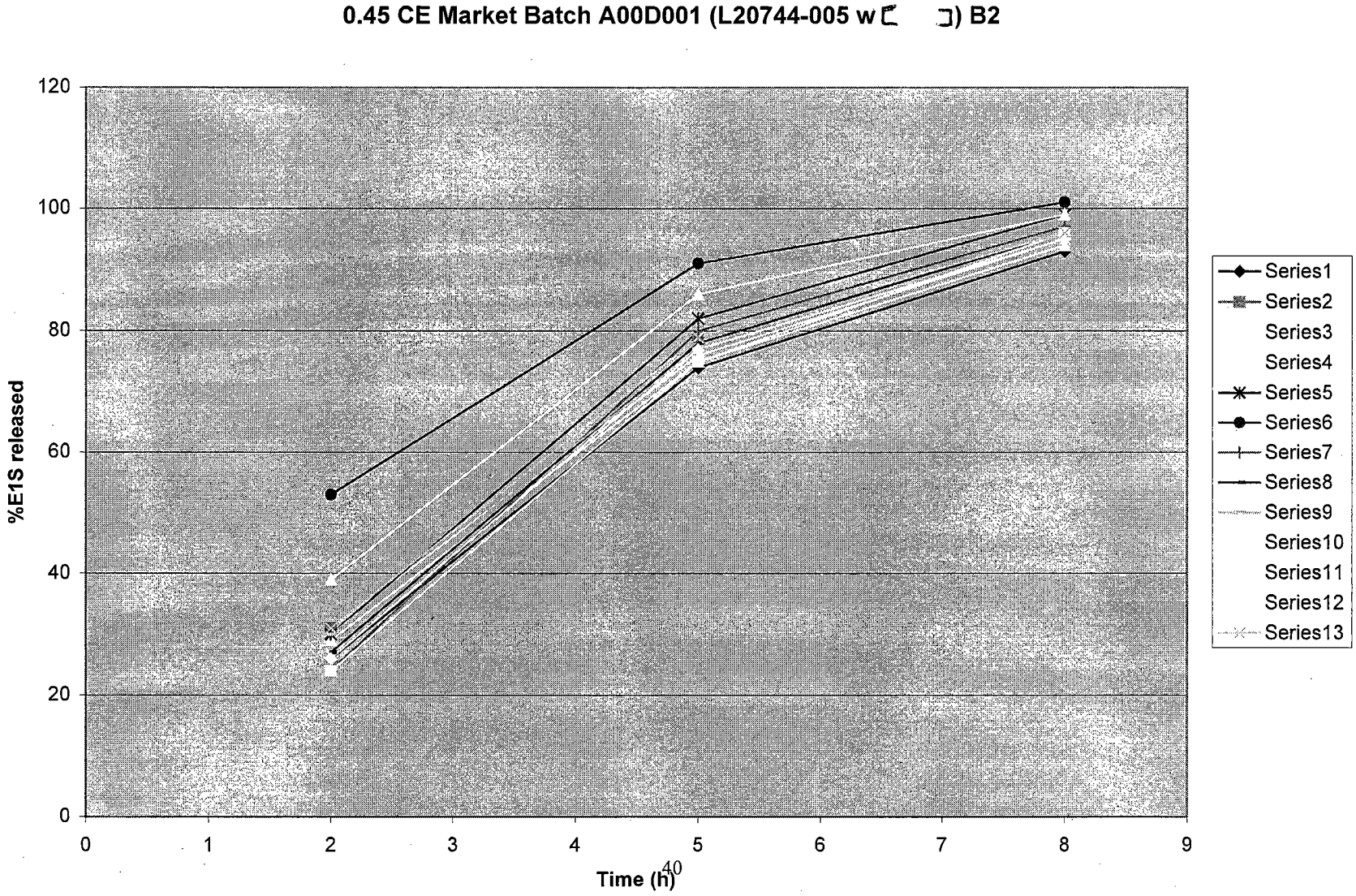
Series19
Series20
Series21
Series22
Series23
Series24
Series25


0.45 CE Market Batch A00D003 (3256-178 w/o) B1
%E1S released
Time (h)
0
20
40
60
80
100
120
0
1
2
3
4
5
6
7
8
9
Series1
Series2
Series3
Series4
Series5
Series6
Series7
Series8
Series9
Series10
Series11
Series12
Series13


0.45 CE Market Batch A00D001 (L20744-005 w B2)
%E1S released
Time (h)
0
20
40
60
80
100
120
0
1
2
3
4
5
6
7
8
9
Series1
Series2
Series3
Series4
Series5
Series6
Series7
Series8
Series9
Series10
Series11
Series12
Series13

f2 Dissolution Comparison

Time	A1	A2	A3	A4	B1	B2	B3
	2	22	22	58	45	38	31
	5	82	80	97	88	87	79
	8	97	97	100	98	100	96

	A1:B1	A1:B2	A1:B3	A2:B1	A2:B2	A2:B3	A3:B1	A3:B2	A3:B3	A4:B2
f2		50.3			63.6		44.4			50.6

All 0.45 mg conjugated estrogens tab
A1 = clinical batch 3TEL (3256-178 w/o[ ])
A2 = clinical batch 3TEL (L20744-005 w[ ])
A3 = clinical batch 1997B0091 (3256-178 w/o[ ])
A4 = clinical batch 1997B0091 (L20744-005 w[ ])
B1 = market batch A00D003 (3256-178 w/o[ ])
B2 = market batch A00D001 (L20744-005 w[ ])

3 page(s) of draft labeling has been removed from this portion of the review.

Clinical Pharmacology/Biopharmaceutics Review (7/25/01)

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

/s/

S.W. Johnny Lau
7/24/01 06:55:16 PM
BIOPHARMACEUTICS

Ameeta Parekh
7/25/01 10:28:19 AM
BIOPHARMACEUTICS
I concur

Filing Memo

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW	
NDA:	**04-782 SE2-115**
To:	**HFD-580**
Place:	PKLN 17B43
Compound:	0.45 mg conjugated estrogens
Sponsor:	Wyeth-Ayerst Research
Date:	September 19, 2000, 10:00 a.m. PKLN 17B43
From:	S.W. Johnny Lau, R.Ph., Ph.D.

Background:

NDA 04-782 SE2-115 (related to IND 21,696) for the 0.45 mg conjugated estrogens (CE) oral tablet was submitted on July 31, 2000. This sNDA concerns the low dose CE alone tablet, for the treatment of moderate to severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy. Sponsor also submitted NDA 20-527 SLR-017 for 0.45 mg CE/1.5 mg medroxyprogesterone acetate (MPA) [redacted] oral tablets on June 15, 2000 for the same indications. Sponsor currently markets PREMARIN® and PREMPRO™. PREMARIN® contains 0.3, 0.625, 0.9, 1.25, and 2.5 mg CE alone oral tablets. PREMPRO™ contains 0.625 mg CE/2.5 mg MPA or 0.625mg CE/5 mg MPA oral tablets. PREMARIN® is derived from pregnant mares' urine, which contains more than 10 estrogens, including the sodium sulfate conjugates of estrone, equilin, 17α-dihydroequilin, 17β-dihydroequilin, 17α-estradiol, 17β-estradiol, equilenin, 17α-dihydroequilenin, 17β-dihydroequilenin, and $\Delta^{8,9}$-dehydroestrone. MPA is a synthetic progestin derived from 17α-hydroxyprogesterone.

Comments:

1. Sponsor conducted a study (0713D2-119-US/GMR-32506) to support the Human Pharmacokinetics and Bioavailability section of NDA 04-782 SE2-115 (see Attachment). This study also supports the recently submitted NDA 20-527 SLR-017.
2. Study 0713D2-119-US/GMR-32506 was a randomized, single-dose, 4-period/treatment, crossover study that assessed the relative bioavailability (BA) of estrogens and MPA from 2 x 0.625 mg CE/2.5 mg MPA, 2 x 0.45 mg CE/2.5 mg MPA, 2 x 0.45 mg CE/1.5 mg MPA, and 2 x 0.45 mg CE alone oral tablets.
3. Sponsor conducted a clinical safety and efficacy study (0713D2-309-US/GMR-38605) to support NDA 04-782 SE2-115.
4. Bioanalytical report (0713D2-119-US/GTR-31208) together with validation report for the determination of unconjugated and total estrone (baseline adjusted and unadjusted), equilin, 17β-estradiol (baseline adjusted and unadjusted), 17β-dihydroequilin, $\Delta^{8,9}$-dehydroestrone, and 17β-$\Delta^{8,9}$-dehydroestradiol in plasma via GC/MS/MS for the clinical pharmacokinetics (PK) study was provided (volume 20 of 65).
5. Clinical PK study report (0713D2-119-US/GMR-32506) was provided (volume 13 of 65).
6. In vitro dissolution methods and data for CE from various CE tablet formulations used in the clinical safety and efficacy as well as PK studies were provided (Table 6.1.5A; volume 12 of 65); however, those data were based on the USP 22 and 23 methods (disintegration apparatus, simulated gastric fluid media, and 15 minutes time points for 1 hour of content released) for conjugated estrogens tablets. The proposed in vitro dissolution methods and specifications for the 0.45 mg CE tablet are in accordance with the 0.3 and 0.625 mg CE marketed products. The marketed CE

products are tested via the USP 24 method (USP Apparatus 2, water as medium, and at 2, 5, and 8 hours time points of content released). The difference in in vitro dissolution methods is a review issue. Reviewing chemist, David Lin, found the in vitro dissolution data for the batch 0930287B/3TEL (used in the clinical pharmacology study 0713D2-119-US), based on the USP 24 method in the Chemistry, Manufacturing, and Control section.

7. The formulations (CE and CE/MPA) tested in the clinical pharmacology study 0713D2-119-US are identical to the marketed formulations in terms of scale of manufacture and composition except the color coat, which was white in the clinical formulation (Section 6.1.3; volume 12 of 65). No information is provided whether the formulations tested in the clinical safety and efficacy study are identical to the to-be-marketed formulation. Comparisons of in vitro dissolution data based on the USP 24 method for the formulation tested in the clinical safety and efficacy study versus that of the to-be-marketed formulation were also not provided.
8. Labeling for the Clinical Pharmacology section was provided (volume 3 of 65). However, no references were provided for the labeling, except 1 annotation of internal study report (0713D2-309-US/GMR-38605). No substantiation was provided for the difference between the proposed and the current PREMARIN® Clinical Pharmacology labeling.
9. PK data for study 0713D2-119-US/GMR-32506 in electronic diskettes (ASCII format) with user guide as well as study reports and Human Pharmacokinetics and Biopharmaceutics summary in Word 97 software files will aid the NDA review.

Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) found that the Human Pharmacokinetics and Bioavailability section of NDA 04-782 32-115 is fileable. Comments 7 to 9 above should be communicated to and addressed by the sponsor.

Johny Lau October 3, 2000

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

FT signed by Ameeta Parekh, Ph.D., Team Leader Ameeta Parekh 10/3/00

cc: NDA 04-782, HFD-870 (H. Malinowski, J. Hunt, A. Parekh, J. Lau); HFD-580 (T. van der Vlugt, D. Lin, D. Moore), CDR (B. Murphy for Drugs)

Item 6.1 and Item 8.3.1: Human Pharmacokinetics and Bioavailability Summary

TABLE 6.1.2.A. DESCRIPTION OF STUDY 0713D2-119-US

Protocol No. Report No. (Investigator)	Study Design	Dose	Batch No.	No. in PK Analysis {sex}[a] [ethnic][b] {age}[c]	Applicant Conclusion
0713D2-119-US GMR-32506 [redacted]	Single-dose, phase I study of the comparative bioavailability of estrogens and MPA from 3 strengths of CE/MPA combination tablets and 1 strength of a tablet of CE alone	CE/MPA Group A: 2 x 0.625 mg/2.5 mg Group B: 2 x 0.45 mg/2.5 mg Group C: 2 x 0.45 mg/1.5 mg CE alone Group D: 2 x 0.45 mg	A: 2TQA B: 3TEN C: 3TEM D: 3TEL	31 (F) [1W, 34 H] {39 - 65, 57}	Two tablets of CE/MPA 0.45 mg/2.5 mg or 0.45 mg/1.5 mg, or 2 CE 0.45 mg tablets produced lower estrogen concentrations than did 2 combination tablets of 0.625 mg/2.5 mg. MPA concentrations were lower with CE/MPA 0.45 mg/1.5 mg than with 0.625 mg/2.5 mg or 0.45 mg/2.5 mg. Estrogens and MPA behaved pharmacokinetically in a dose-related manner.

a: Sex: F = female.
b: Ethnic origin: W = white, H = Hispanic
c: Age: min - max; mean in years

Appears This Way
On Original

Attachment

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

/s/

S.W. Johnny Lau
7/24/01 06:58:30 PM
BIOPHARMACEUTICS

Ameeta Parekh
7/25/01 10:21:47 AM
BIOPHARMACEUTICS
I concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 04-782/S-115 & S-130

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA #04-782____ SUPPL # 115_____
Trade Name Premarin Generic Name conjugated estrogens USP
Applicant Name Wyeth Pharmaceuticals HFD-580___
Approval Date April 24, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_✔__/

   b) Is it an effectiveness supplement? YES /_✔__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE-2_____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /___/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

   d) Did the applicant request exclusivity?

YES /___/ NO /__✔_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_✔__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_✔__/

If yes, NDA # _____ Drug Name _____

_

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_✔__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_✔__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 04-782_____ Premarin_____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /__✔_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_✔__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_✔__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_✔__/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_✔__/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_✔__/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 0713D2-309-US_____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /_✔__/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # 20-527_____ Study #0713D2-309-US_____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_✔__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 21,696 YES /✓/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_✔__/

If yes, explain: _____

_____

_____

Kassandra Sherrod, R.Ph. 4/24/03
Signature of Preparer Date
Title:Regulatory Project Manager

_____ _____
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Daniel A. Shames
4/24/03 10:21:52 AM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # :04-782 Supplement Type (e.g. SE5):SE2_____ Supplement Number: 115

Stamp DateOctober 16, 2002:_____ Action Date: April 30, 2003

HFD 580 Trade and generic names/dosage form: Premarin (conjugated estrogens USP) tablets

Applicant: Wyeth Pharmaceuticals Therapeutic Class: hormone replacement

Indication(s) previously approved: treatment of moderate to severe vasomotor symptoms associated menopause , and treatment of vulvar and vaginal atrophy

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: treatment of vasomotor symptoms, vulvar and vaginal atophy

Is there a full waiver for this indication (check one)?

✔ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
✔ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns

- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

Kassandra Sherrod, R.Ph.
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi

HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: January 29, 2001

From: Kim Colangelo
Senior Regulatory Associate
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 20-527/S-017
NDA 4-782/S-115

I have reviewed the financial disclosure information submitted by Wyeth-Ayerst Laboratories in support of their supplemental NDAs, NDA 20-527/S-017 and NDA 4-782/S-115.

One study was conducted to support the safety and efficacy of Prempro/Premphase (NDA 20-527/S-017) and Premarin (NDA 4-782/S-115) for the treatment of vasomotor symptoms associated with menopause, and vulvar and vaginal atrophy. The study number and the results of the review of financial disclosure documents are summarized below:

Study Number/Title	Study Status	Financial Disclosure Review
Study 309-US, "Health and Osteoporosis, Progestin and Estrogen Study"	Ongoing as of February 2, 1999	Appropriate documentation received, financial disclosure does not impact study outcome

Documents Reviewed:

- Financial Certification and Disclosure Information submitted June 15, 2000 (NDA 20-527/S-017) and July 31, 2000 (NDA 4-782/S-115)
- Facsimile to Ms. Lana Pauls dated July 19, 2000 containing number of patients per site with non-compliant investigators (attached)
- Financial Certification and Disclosure Information submitted November 22, 2000 (NDA 20-527/S-017 and NDA 4-782/S-115)

In addition, clarification of several points in these documents was requested via telephone on January 25, 2001. Verbal response was received from the sponsor on January 26, 2001. Specifically:

1. Regarding the July 19, 2000 facsimile:
   a) The number of patients enrolled per subinvestigator is actually per site. For example, a total of 16 patients were seen at Site 58, which had six non-compliant subinvestigators, not 16 patients per subinvestigator.
   b) The number of patients at Site 13 (Principal Investigator Reindollar) was six, not 13 as listed for (sub) Investigator[ ]
   c) The number of patients analyzed was 2,673. The term "analyzed" is equivalent to the terms "active" and "completed" used in individual financial disclosure statements.

d) The number of patients enrolled was 2,805.

2. Regarding the October 17, 2000 submission
   a) [ ] was added as a (sub)investigator in an August 30, 2000, submission, which is why his name did not appear on the initial certification dated March 17, 2000.

Study 309-US

There were 323 principal and subinvestigators (investigators) in this trial. Seventeen investigators at ten sites enrolling 16.0% of the total patients enrolled did not submit financial certification or disclosure documents to the sponsor. Of the remaining investigators who complied, five had disclosable information. They are summarized as follows:

- [ ] received approximately $28,000 from the sponsor for her participation in the visiting Professor Program and for travel reimbursement. [ ] was a principal investigator with ten subinvestigators at a site which enrolled [ ] patients ([ ]% of the total enrolled.)
- [ ] received approximately $28,000 from the sponsor for his participation in the visiting Professor Program and for travel reimbursement. [ ] was a principal investigator with two subinvestigators, and enrolled [ ] patients ([ ]% of the total enrolled.)
- [ ] received approximately $25,000 from the sponsor for his participation in the visiting Professor Program and for travel reimbursement. [ ] was a principal investigator with ten subinvestigators, at a site that enrolled [ ] patients ([ ]% of the total enrolled.)
- [ ] is a member of the Board of [ ] Corporation, and as such, holds 4,936 shares of common stock and phantom stock units representing the economic equivalent of approximately 13,829 shares of common stock. In addition, a member of her immediate family holds 50 shares of common stock. [ ] assumed the role of principal investigator upon the resignation of the original principal investigator. A total of [ ] patients ([ ]% of the total enrolled) were enrolled at this site, [ ] prior to [ ] arrival.
- [ ] holds over $50,000 in stock in American Home Products. He is a subinvestigator with a principal investigator and five other subinvestigators at a site that enrolled [ ] patients ([ ]% of the total enrolled.)

The sponsor employed the following mechanisms in an attempt to obtain Financial Disclosure forms from investigators:

- telephone calls to the sites and/or universities requesting additional information on the investigators,
- faxes to sites which indicated that a forwarding address was available,
- faxes to locations found as a result of Internet searches,
- Medical Monitor contact from previous professional associations,
- Internet searches of personnel directories of professional organizations such as ACOG, and
- e-mails to sites where addresses could be found.

Conclusion:

Adequate documentation was submitted to comply with 21 CFR 54. The sponsor has acted with due diligence in attempting to obtain documentation from non-compliant investigators and the rate of return is acceptable. The information disclosed is not significant enough to impact the study outcome.

FACSIMILE TRANSMISSION
WYETH-AYERST RESEARCH
170 RADNOR-CHESTER ROAD
ST. DAVIDS, PA 19087

Telefax Number: (610) 964-5973

DATE: *July 19, 2000*

TO: ***Lana Pauls, Associate Director***
Division of Reproductive and Urologic Drug Products

FACSIMILE No: ***1-301-827-4267***

FROM: *JoAnne M. Bissinger*
Worldwide Regulatory Affairs (610) 902-3731

No. of PAGES: *2 (including cover page)*

Re. ***NDA No. 20-527 S-017***

Lana,

As you requested this morning, I am providing you with a table that lists investigators that did not provide Financial Disclosure forms, their site [(site number (principle investigator)] and the number of patients enrolled at the site. In addition the total number of patients that were analyzed is given. See the attached table.

If you have any questions, please contact me at the above referenced telephone number.

Regards.

JoAnne M. Bissinger
Manager, Worldwide Regulatory Affairs

DRUDP.fax

NDA No. 20-527 S-017
Conjugated Estrogens/Medroxyprogesterone Acetate Tablets

Investigator	Site # (Principe Investigator)	No. of Patient
[redacted]	58 (Mezitis)	16
	58 (Mezitis)	16
	58 (Mezitis)	16
	58 (Mezitis)	16
	25 (Moghissi)	77
	25 (Moghissi)	77
	57 (Lobo)	65
	04 (Polan)	40
	62 (Dumesic)	48
	34 (Calkins)	72
	33 (Ravnikar)	03
	46 (Kessel)	39
	17 (Fossum)	45
	46 (Kessel)	39
	26 (Kubik)	19
	22 (Homesley)	21
	44 (Utian)	113
	26 (Kubik)	19
	29 (Pinkerton)	64
	25 (Moghissi)	77
	20 (Harrington)	14
	58 (Mezitis)	16
	46 (Kessel)	39
	57 (Lobo)	65
	61 (Liu)	29
	03 (Bachmann)	23
	62 (Dumesic)	48
	06 (Bush)	46
	58 (Mezitis)	16
	04 (Polan)	40
	58 (Mezitis)	16
	35 (Schaff)	28
	61 (Liu)	29
	13 (Reindollar)	06
	02 (Archer)	73
	06 (Bush)	46
	37 (Shoupe)	95
	17 (Fossum)	45
	13 (Reindollar)	13

2,673 patients were analyzed

/s/

Kim Colangelo
2/5/01 11:28:38 AM
CSO

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
DA 4-782	Efficacy Supplement Type SE2-	Supplement Number 115
Drug:Premarin (conjugated estrogens, USP)	Applicant:Wyeth Pharamceuticals, Inc.	
RPM:Kassandra Sherrod/Margaret Kober	HFD-580	Phone # 301-827-4260
Application Type: (✔) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(✔) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	May 31, 2001,July 31, 2001,April 30, 2003
❖ Special programs (indicate all that apply)	(✔) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(✔) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (✔) No
• This application is on the AIP	( ) Yes ( ) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(✔) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(✔) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	✔

❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ Actions	
• Proposed action	(✔) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE 7/31/01
• Status of advertising (approvals only)	(✔) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (✔) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(✔) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	✔
• Most recent applicant-proposed labeling	✔
• Original applicant-proposed labeling	✔
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	Mtg. 3/10/03
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	✔
• Reviews	✔
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✔
❖ Memoranda and Telecons	✔
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Statistical Information	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	4.24.03
❖ Clinical review(s) *(indicate date for each review)*	4.24.04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	7.18.2001 in Med. Officer review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	✔
❖ Statistical review(s) *(indicate date for each review)*	3/18/01
❖ Biopharmaceutical review(s) *(indicate date for each review)*	7.25.01
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/a
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	7/9/01, 7/26/01, 7/30/01, 4/18/03
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	See CMC review 7/7/01
• Review & FONSI *(indicate date of review)*	N/a
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: (✔) Acceptable ( ) Withhold recommendation
❖ Methods validation	(✔) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A-

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 4782/S-115
NDA 4782/S-137
NDA 4782/S-141
NDA 4782//S-142

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

Dear Applicant:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Premarin.

Since 2000, FDA has conducted several comprehensive inspections of bioequivalence studies in which the bioanalytical analysis was conducted by [ ]. The findings of these inspections raise significant concerns about the validity of the reported results of these analytical studies conducted in support of drug applications for marketing. Our findings from these inspections include, but are not limited to, the following:

- Failure to conduct a systematic and thorough evaluation to identify and correct sources of contamination.
- Failure to investigate anomalous results.
- Lack of assay reproducibility between original and repeat results.
- Assay accuracy not assured under the conditions of sample processing.
- Biased exclusion of study data resulting in the acceptance of failed runs.
- Failure to demonstrate the accuracy of analytical methods with appropriate validation experiments and documentation.

As a result of these findings, [ ] agreed to conduct an audit of data from all its bioequivalence studies generated from January 2000 to December 2004. However, FDA identified significant deficiencies with the [ ] audit during its most recent inspection. Thus, serious questions remain about the validity of any data generated by [ ] in studies during this time period that have not been inspected by FDA. In view of these findings, FDA is informing holders of approved NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, pharmacokinetic, drug-drug interaction and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us within 30 days of receipt of this letter if you have submitted any studies conducted by [ ] during the time period of concern (January 2000 through December 2004). Please submit information on each of the studies submitted, including supplement number (if appropriate), study name/protocol number, and date of submission. This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

Once we have made an assessment regarding the potential impact of these data, we will contact you regarding the steps that need to be taken, if any, to assure the accuracy of the data submitted to your application.

If you have any questions, call Ayoub Suliman, Regulatory Project Manager, at 301-796-0630.

Sincerely,

{See appended electronic signature page}

Scott Monroe, MD
Director (Acting)
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Maria Walsh
1/24/2007 11:02:16 AM
For Division Director

Division of Reproductive and Urologic Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: 04-782/S-115, S-130

Name of Drug: Premarin® (conjugated estrogens tablets, USP)

Applicant: Wyeth Pharmaceuticals

Material Reviewed:

Submission Date(s): May 22, 2003

Receipt Date(s): May 27, 2003

Background and Summary

The sponsor was sent an approval letter dated April 24, 2003, requesting final printed labeling.

Review

The sponsor has submitted final printed labeling identical to the labeling in the approval letter.

Conclusions

The FPL is acceptable. The sponsor should be sent an acknowledge and retain letter.

Kassandra Sherrod, R.Ph.
Regulatory Health Project Manager

Drafted:KS/6.19.03
Revised/Initialed: Shames, 6.24.03
Finalized: Sherrod, 6.26.03
Filename: c:/data/mydocs/nda/04782/S130ret.rev

RPM LABELING REVIEW

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/s/

Kassandra C. Sherrod
7/9/03 04:06:54 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 04-782/S-115, S-130

Wyeth Pharmaceuticals Inc.
Attention: Nanette E. Holston
Director, Global Brand Management
Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Holston:

We acknowledge receipt of your May 22, 2003, submissions containing final printed labeling in response to our April 24, 2003, letter approving your supplemental new drug applications for Premarin® (conjugated estrogens tablets, USP).

We have reviewed the labeling that you submitted in accordance with our April 24, 2003, letter and we find it acceptable.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Daniel A. Shames
7/16/03 03:13:59 PM

Memorandum of Teleconference

Date: February 6, 2003

Time: 10:00 AM

Application: NDAs 20-527/S-017 and 04-782/S-115

Participants:

From Wyeth:

Ginger Constantine, MD, Vice-President Women's Healthcare CR&D
Joseph Sonk, PhD, Assistant Vice-President Women's Healthcare, WWRA
Diane Harrison, MD, Director, Women's Healthcare, CR&D
Robert Northington, PhD, Director, Clinical Biostatistics, CR&D
Simon Golec, PhD, Director, Women's Healthcare, CMC, WWRA
Jennifer Norman, Associate Director, Women's Healthcare, WWRA
Colleen Murray, Senior Regulatory Coordinator, Women's Healthcare, WWRA

From DRUDP:

Theresa van der Vlugt, M.D., M.P.H. – Repro, Medical Officer, DRUDP (HFD-580
Kassandra Sherrod, R.Ph., Regulatory Project Manager
David Lin, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Sarah Pope, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Background
The supplemental application 20-527/017 was resubmitted on September 11, 2002, received on September 12, 2002. The supplement proposes the use of 0.45 mg conjugated estrogen and 1.5 mg medroxyprogesterone acetate combination tablets in a continuous combined regimen for the treatment of moderate to severe vasomotor symptoms associated with the menopause and the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. The User Fee goal date is March 12, 2003. An approvable action was taken by DRUDP on April 13, 2001.

The supplemental application 04-782/S115 was resubmitted on October 28, 2002, received October 30, 2002. The supplement proposes the use of Premarin 0.45 mg for the treatment of moderate to severe vasomotor symptoms associated with the menopause and the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. The User Fee goal date is April 30, 2003. An approvable action was taken by DRUDP on July 31, 2001.

Meeting Objective:
To review the recommended changes to the Prempro SLR-017 draft labeling and the Premarin SLR-115 draft labeling.

Discussion Points:

- See attached labeling; additions are indicated by double underline and deletions are indicated by ~~strike-through~~.

Action items:

- Sponsor will revise Tables 1, 2, and 3 of the Prempro label and submit.
- Sponsor will send SAS dataset for the proposed cumulative amenorrhea figure for Prempro.
- Sponsor will revise Tables 1 and 2 of the Premarin label and submit.
- Discussion on reclassification.

Signature, minutes preparer

Signature, Chair

cc: Original
HFD-580/20-527 Div. Files
HFD-580/04-782/Div Files
HFD-580/Slaughter, van der Vlugt, Lin, Pope, Parekh

Drafted: by KS/3.04.03
Initialed by:van der Vlugt, Pope, 3.5.03
Final: Sherrod, 3.10.03
TELECONFERENCE MEETING MINUTES

Memorandum of Meeting Minutes

Date:	February 4, 2003
Time:	10:30 AM
Application:	NDAs 20-527/S-017 and 04-782/S-115
Place:	Parklawn; 17B-43
Type of Meeting:	5-month status/labeling meeting
Meeting Chair:	Shelley R. Slaughter, M.D., Ph.D.
Meeting Recorder:	Kassandra Sherrod, R.Ph.

FDA Attendees:
Shelley Slaughter, M.D., Clinical Team Leader, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., Medical Officer, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Kassandra Sherrod, Project Manager, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
David Lin, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II)@ DRUDP (HFD-580)
Sarah Pope, Ph.D., Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Background
The supplemental application ~~20-527~~/017 was resubmitted on September 11, 2002, received on September 12, 2002. The supplement proposes the use of 0.45 mg conjugated estrogen and 1.5 mg medroxyprogesterone acetate combination tablets in a continuous combined regimen for the treatment of moderate to severe vasomotor symptoms and treatment of vulvar and vaginal atrophy associated with menopause. The User Fee goal date is March 12, 2003. An approvable action was taken by DRUDP on April 13, 2001.

The supplemental application 04-782/S115 was resubmitted on October 28, 2002, received October 30, 2002. The supplement proposes the use of Premarin 0.45 mg for the treatment of moderate to severe vasomotor symptoms and treatment of vulvar and vaginal atrophy associated with menopause.The User Fee goal date is April 30, 2003. An approvable action was taken by DRUDP on July 31, 2001.

Meeting Objective:
To review labeling comments for supplements 115 and 017.

Discussion Points:

- See attached labeling; additions are indicated by double underline and deletions are indicated by ~~strike through~~.

Action items:

- PM to schedule T-Con with sponsor to discuss revisions made in the attached label.

55

Signature, minutes preparer

Signature, Chair

60

65

cc: Original
HFD-580/20-527 Div. Files
HFD-580/04-782/Div Files
HFD-580/Slaughter, van der Vlugt, Lin, Pope

70

Drafted: by KS/2.20.03
Initialed by van der Vlugt, 2.21.03/Lin, 2.27.03/Slaughter, Pope, 3.3.03
Final: Sherrod/3.3.03
MEETING MINUTES

75

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 04-782/S-115

ACKNOWLEDGEMENT LETTER

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

Dear Ms Norman:

We acknowledge receipt on October 30, 2002 of your October 28, 2002 resubmission to your supplemental new drug application for Premarin (conjugated estrogens tablets, USP).

We consider this a complete, class 2 response to our July 31, 2001, action letter. Therefore, the user fee goal date is April 30, 2003.

If you have any question, call George Lyght, R. Ph., Regulatory Project Manager at (301) 4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R. Ph.
Chief, Project Management Staff
Division of Reproductive and
Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
12/16/02 04:52:38 PM
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES
New York District

Food & Drug Administration
300 Pearl Street, Suite 100
Buffalo, NY 14202

July 26, 2001

D. Bruce Burlington, M.D.
Senior Vice President
Wyeth-Ayerst Pharmaceuticals
Worldwide Regulatory Affairs and Compliance
150 Radnor-Chester Road
St. Davids, PA 19087

Dear Dr. Burlington:

This letter constitutes a reply to Wyeth's written FDA-483 responses and other inspection related communications covering Premarin. Our comments are as follows.

1) Regarding an **August 25, 2000** letter from Mr. W.E. Brooks, Managing Director, et al, to Ms. Brenda Holman, District Director, concerning an FDA inspection conducted at Rouses Point, New York, July 10 – 21, 2000:

While a number of the observations listed on the FDA-483, Inspectional Observations, appear to be resolved, the response to observation 5 remains unsatisfactory. Your response confirms that, since 1986, Wyeth has used in-process samples collected from [ ] following application of the [ ] for the purpose of testing for batch release. You only committed to a correction until December 31, 2000, pending your re-examination of the practice. CGMP (21 CFR 211.160 and 211.165) requires that samples of finished product representing finished batches be tested for the purpose of batch release. In fact, your firm performed release testing of product sampled prior to completion of final processing steps. You should test in-process material such as [ ] tablets for dissolution, as well as test samples of the final coated and branded tablets for dissolution prior to, and in support of, a decision to release the batch.

Furthermore, this practice raises questions concerning the value of the dissolution profile data you collected from 1986 to the time you ended the practice. Include in your response to this office a description of your current practice of sampling for batch release testing for dissolution.

Although it was not listed as an observation on the FDA-483 issued July 21, 2000, the investigator documented that your master and batch control records for all strengths lack detailed sampling instructions to cover the in-process sampling of tablets from the [ ]. This observation was discussed with a manager and may have been corrected. Please advise this office if this observation has been corrected. If it has not been, please do so and advise this office of the action taken.

2) Regarding a **February 21, 2001** letter from Mr. John Bucceri, Senior Vice President, Global Supply Chain and yourself, to Mr. Jerome Woyshner, Acting District Director, concerning an FDA inspection conducted at Rouses Point, New York, January 22 – February 1, 2001:

We remain concerned about the adequacy of process controls, specificity, and documentation. In addition to the examples listed under observation 1, included on the FDA 483 are other examples such as failure to monitor and control the [ ] (observation 2), and failure to provide adequate instructions in Master and Control Records for proper [ ] following application of the [ ] (observation 6). Together, these observations support our conclusion that controls are not in place allowing for adequate process validation.

In addition, your written response fails to globally address whether, in addition to Premarin, other products will be assessed to determine if manufacturing controls and documentation are similarly deficient. The need for your firm to address CGMP deviations globally was also discussed during our June 8, 2001, regulatory meeting.

We acknowledge your firm's commitment not to distribute batches in the event that one or more [ ] fail to meet dissolution test specifications. Your letter states that you will further analyze this issue. Please advise us of any change in your approach on this issue.

3) Regarding letter dated **February 28, 2001,** from Mr. John Bucceri, Senior Vice President, Global Supply Chain and yourself, to Ms. Mildred Barber, District Director, San Juan District, concerning an inspection conducted at Guayama, Puerto Rico, January 8 – February 12, 2001:

We are commenting on behalf of FDA's San Juan District. Your letter indicates that your firm only performs in-process assessment of conformance to the mean of key tablet attributes such as weight and hardness. In order to detect emerging process problems (e.g., a single defective punch causing an atypically low tablet weight trend) in a timely manner and ensure ongoing process control, individual tablet results should also be monitored and evaluated against established process specifications.

In addition, in-process product failing mean or individual control specifications should be routinely segregated for disposition by the quality control unit.

4) Regarding validation commitments included, and certain manufacturing practices discussed, within response letters dated **August 25, 2000,** and **February 21, 2001:**

Both letters commit to a process of revalidating all strengths of Premarin by the end of 2001. We also note that your timeframe for investigating process improvements and/or reformulation in order to address Premarin quality problems extends into 2005. Please provide up-to-date information on your efforts for identifying the root cause for release and stability dissolution failures, and if these efforts have not been successful, explain how this impacts on your re-validation program (e.g., include and explain any change in your timeline to revalidate all drug product strengths).

Your written responses of August 25, 2000, and February 21, 2001, also cite approvals obtained through NDA submissions. To avoid any further misunderstandings, please be aware that approvals of such submissions by the Agency in no way constitute approvals of practices as they relate to compliance with the requirements of CGMPs.

5) In addition to our inspectional communications, meetings have occurred and other correspondence has issued. We are in receipt of a letter dated **June 18, 2001**, from Dr. Nirdosh Jagota, Director, Worldwide Regulatory Affairs, with attachments, to Dr. Ajaz Hussain, Acting Deputy Director, Office of Pharmaceutical Sciences concerning Premarin.

The letter references and contains information requested at a regulatory meeting in Rockville, Maryland, on June 8, 2001, between Wyeth-Ayerst, the Center for Drug Evaluation and Research, San Juan District, and New York District. This letter discusses your long-term plans for continued marketing of Premarin. While this correspondence remains under consideration, we have found the lengthy timelines for corrective actions to be of general concern.

Please feel free to contact William J. Thompson of the New York District Office if you have any questions regarding this letter. In addition, please provide copies of your response to this letter to Ajaz S. Hussain and Joseph C. Famulare of the Center for Drug Evaluation & Research.

Edward Thomas
Acting District Director,
New York District

Joseph C. Famulare
Director, Division of
Manufacturing &
Product Quality
CDER

Ajaz S. Hussain, Ph.D.
Acting Deputy Director,
Office of Pharmaceutical Science
CDER

CC:

John V. Bucceri
Senior Vice President, Global Supply Chain
Wyeth-Ayerst Pharmaceuticals
Worldwide Regulatory Affairs and Compliance
150 Radnor-Chester Road
St. Davids, PA 19087

Internal CC's:

D Kolaitis, HFR-NE1
District Director, HFR-NE100
Compliance Director, HFR-NE140
J Thompson, HFR-NE350

KCampbell, HFR-MA140 (FYI)

J Woyshner, HFR-NE150 *[EF 1310337]*
J Erdmann, (Syracuse RP), HFR-NE3550
M Barber (SJN-DO), HFR-SE500
M Mason, HFR-SE540

A Hussain, HFD-003
S Allen, HFD-580
M Rhee, HFD-580
D Lin, HFD-580
D Moore, HFD-580

J Hunt, HFD-870

D Horowitz, HFD-300
Chron File, HFD-325 (Wyeth Premarin)

J Famulare, HFD-320
F Blumenschein, HFD-325
B Hasselbalch, HFD-325
P Alcock, HFD-324
R Friedman, HFD-325

DRAFT:	WThompson
COMMENTS:	SAllen, BHasselbalch, RFriedman, WThompson,
REVISION:	RFriedman, AHussain, JFamulare
FINAL:	RFriedman

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 4782/115
Stamp: 31-JUL-2000
Regulatory Due: 31-MAY-2001
Applicant: WYETH AYERST LABS
8299
PHILADELPHIA, PA 191018299
Priority: 1S
Org Code:

Action Goal:
District Goal: 26-APR-2001
Brand Name: PREMARIN TABLETS
Estab. Name:
Generic Name: ESTROGENS, CONJUGATED

Dosage Form: (TABLET)
Strength: SEE COMMENTS

FDA Contacts: D. MOORE (HFD-580) 301-827-4236 , Project Manager
D. LIN (HFD-580) 301-827-4230 , Review Chemist
M. RHEE (HFD-580) 301-827-4237 , Team Leader

Overall Recommendation: WITHHOLD on 26-JUL-2001 by P. LEFLER (HFD-324) 301-827-0062

Establishment: 9613692
AYERST ORGANICS INC
R7A 7H2
BRANDON, MANITOBA, CA

DMF No: AADA:
Responsibilities: INTERMEDIATE MANUFACTURER
Profile: CEX OAI Status: NONE
Estab. Comment: MANUFACTURES THE INTERMEDIATE MATERIAL [redacted] (on 18-SEP-2000 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-SEP-2000				LINDAV
SUBMITTED TO DO	19-SEP-2000	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	21-SEP-2000	GMP			ADAMSS
INSPECTION PERFORMED	27-NOV-2000		31-OCT-2000		EGASM
DO RECOMMENDATION	19-DEC-2000			ACCEPTABLE INSPECTION	ADAMSS
OC RECOMMENDATION	21-DEC-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment: 2650135
AYERST WYETH PHARMACEUTICALS
STATE ROAD 3 KM 142.1
GUAYAMA, PR 00784

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: TCT OAI Status: NONE
Estab. Comment: PERFORMS [redacted] PERFORMS BRANDING AND PACKAGING. (on 18-SEP-2000 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-SEP-2000				LINDAV
SUBMITTED TO DO	19-SEP-2000	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	11-OCT-2000	PS			MTORRES
INSPECTION SCHEDULED	23-JAN-2001		22-FEB-2001		MTORRES
INSPECTION PERFORMED	02-MAR-2001		12-FEB-2001		MTORRES
EIR READY FOR ENDORSEMENT.					
DO RECOMMENDATION	02-MAR-2001			WITHHOLD PEND REG ACTION - WARNING	MTORRES

26-APR-2001

31-MAY-2001
WYETH AYERST LABS
1S
580
Priority:
Org Code:
Application Comment: THE DOSAGE STRENGTHS FOR THIS DRUG PRODUCT TABLET ARE: 0.3, 0.625, 0.9, 1.25 AND 2.5 MG.
THIS SUPPLEMENT IS FOR A NEW DOSAGE STRENGTH TABLET, 0.45 MG.
(on 18-SEP-2000 by D. LIN (HFD-580) 301-827-4230)

LTR
OBJECTIONABLE CONDITIONS FOUND INCLUDE FAILURE TO JUSTIFY IN-PROCESS CONTROLS DURING [ ]; FAILURE TO ENSURE INTEGRITY AND ACCURACY OF RECORDS; INADEQUATE OPERATIONAL QUALIFICATION OF [ ] EQUIPMENT.

OC RECOMMENDATION 26-JUL-2001 ACCEPTABLE ALCOCKP
DEFIC. NOT SUPPORTED BY CDER

SJN ISSUES SURROUNDING PREMARIN ARE BEING HANDLED BY NYK-DO IN THE JULY 25, 2001 (APPROXIMATE) LETTER TO THE APPLICANT ACKNOWLEDGING THE FIRM'S CORRECTIVE ACTIONS AS BEING INADEQUATE. FIRM TRANSFERS THE PREMARIN PRODUCTS BACK AND FORTH FROM GUAYAMA, PR TO ROUSES POINT, NY.

NYK/SJN/CDER HELD A REGULATORY MEETING WITH THE APPLICANT ON JUNE 8, 2001 WHERE FDA INFORMED FIRM'S TOP MANAGEMENT THAT THE LENGTHY TIMELINES FOR CORRECTIVE ACTIONS FOR PREMARIN PRODUCTS TO BE OF A GENERAL CONCERN.

IN ADDITION, IN A LETTER TO THE FIRM (ISSUED APPROXIMATELY 7-25-01) CDER AND NYK-DO WILL INFORM THE FIRM THAT THEIR CORRECTIVE ACTIONS/RESPONSES TO FDA-483'S ISSUED IN BOTH NYK-DO AND SJN-DO, THAT THERE ARE OUTSTANDING CGMP CONCERNS REMAINGING WHICH NEED TO BE ADDRESSED FURTHER. AS SUCH, WYETH-AYERST, OF ROUSES POINT, NY IS FOUND TO BE UNACCEPTABLE FROM A CGMP STANDPOINT FOR ALL PREMARIN PRODUCTS. UF (12 MONTH GOAL) IS 7-31-01.

Establishment: 1310337
WYETH LABORATORIES INC
64 MAPLE ST
ROUSES POINT, NY 12979
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
Profile: CEX OAI Status: NONE
Estab. Comment: MANUFACTURES THE DRUG SUBSTANCE [ ] ALSO TESTS THE [ ] AND THE DRUG [ ] SUBSTANCE. (on 18-SEP-2000 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-SEP-2000				LINDAV

SUBMITTED TO DO	19-SEP-2000 GMP		DAMBROGIOJ
DO RECOMMENDATION	19-MAR-2001	WITHHOLD	JPODSADO
		PEND REG ACTION - WARNING LTR	

NYK-DO IS RECOMMENDING WITHHOLD FOR THIS SUPPLEMENT BASED ON A RECENT FOR CAUSE INSPECTION TO COVER DISSOLUTION FAILURES OF PREMARIN TABLETS. THE INSPECTION WAS CLASSIFIED OAI WITH A REGULATORY RECOMMENDATION FOR A WARNING LETTER. VARIOUS GMP ISSUES PERSIST INCLUDING VALIDATIONS DEFICIENCIES. THE CENTER CONTINUES TO REVIEW PREMARIN RELATED DEFICIENCIES FROM PREVIOUS INSPECTIONS.

EIR RECEIVED BY OC	02-APR-2001		DAMBROGIOJ
OC RECOMMENDATION	26-JUL-2001	ACCEPTABLE	ALCOCKP
		DEFIC. NOT SUPPORTED BY CDER	

WITHHOLD FOR CEX PROFILE CLASS IS NOT JUSTIFIED. MEMO FROM HFD-324 TO FOLLOW. PREMARIN TABLET PROFILE IS CONSIDERED UNACCEPTABLE. CEX PROFILE IS FOR THE INTERMEDIATE[ ] THAT IS PROCESSED FURTHER TOYIED THE DRUG SUBSTANCE.

Profile: TTR OAI Status: POTENTIAL OAI

Estab. Comment: MANUFACTURES THE [ ] ALSO PERFORMS [ ]

PERFORMS PRODUCT TESTING AND RELEASE. BRANDING AND PACKAGING MAY ALSO BE PERFORMED. (on 18-SEP-2000 by D. LIN (HFD-580) 301-827-4230)

PER JOHN PODSADOWSKI, THE PROFILE CLASS CODE SHOULD BE TTR AND NOT TCT. (on 26-MAR-2001 by S. FERGUSON (HFD-324) 301-827-0062)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-SEP-2000				LINDAV
SUBMITTED TO DO	19-SEP-2000 GMP				DAMBROGIOJ
DO RECOMMENDATION	19-MAR-2001			WITHHOLD	JPODSADO
				PEND REG ACTION - WARNING LTR	

NYK-DO IS RECOMMENDING WITHHOLD FOR THIS SUPPLEMENT BASED ON A RECENT FOR CAUSE INSPECTION TO COVER DISSSOLUTION FAILURES OF PREMARIN TABLETS. THE INSPECTION WAS CLASSIFIED OAI WITH A [ ] [ ] VARIOUS GMP ISSUES PERSIST INCLUDING VALIDATIONS DEFICIENCIES. THE CENTER CONTINUES TO REVIEW PREMARIN RELATED DEFICIENCIES FROM THE PAST INSPECTIONS.

EIR RECEIVED BY OC	02-APR-2001		DAMBROGIOJ
OC RECOMMENDATION	26-JUL-2001	WITHHOLD	ALCOCKP
		DISTRICT RECOMMENDATION	

NYK/SJN/CDER HELD A REGULATORY MEETING WITH THE APPLICANT ON JUNE 8, 2001 WHERE FDA INFORMED FIRM'S TOP MANAGEMENT THAT THE LENGTHY TIMELINES FOR CORRECTIVE ACTIONS FOR PREMARIN PRODUCTS TO BE OF A GENERAL CONCERN.

IN ADDITION, IN A LETTER TO THE FIRM (ISSUED APPROXIMATELY 7-25-01) CDER AND NYK-DO WILL INFORM THE FIRM THAT THEIR CORRECTIVE ACTIONS/RESPONSES TO FDA-483'S ISSUED IN BOTH NYK-DO AND SJN-DO, THAT THERE ARE OUTSTANDING CGMP CONCERNS REMAINGING WHICH NEED TO BE ADDRESSED FURTHER. AS SUCH, WYETH-AYERST, OF ROUSES POINT, NY IS FOUND TO BE UNACCEPTABLE FROM A CGMP STANDPOINT FOR ALL PREMARIN PRODUCTS. WITHHOLD APPROVAL UNTIL CORRECTIVE ACTIONS ARE DEEMED SATSIFACTORY. UF (12 MONTH GOAL) IS 7-31-01.

MEMO RE: WITHHOLD OF THIS APPLICATION WILL FOLLOW FROM HFD-324.

Appears This Way
On Original

Teleconference Minutes

Date: June 22, 2001 **Time:** **Location:** Parklawn; 17B-31

NDA 4-782/SE2-115 **Drug:** Premarin Tablets

Indication: VMS

Type of Meeting: Chemistry Information Request

External Constituent: Wyeth-Ayerst

Meeting Chair: David Lin, Ph.D.

Meeting Recorder: David Lin, Ph.D.

FDA Attendees:
David Lin, Ph.D.-Chemist, Division of New Drug Chemistry II (DNDCII) @ Division of Reproductive and Urologic Drug Products (HFD-580)

External Participants:
Ms. Susan Wilson, Worldwide Regulatory Affairs

Purpose of the Meeting:
To request additional information on the proposed container/closure system for the drug product tablets and whether a DMF is available for colorant used in the 0.45 mg strength tablet.

Decisions Made:
- The sponsor agreed to verify the blister film supplier for the blister pack.
- The sponsor agreed to confirm the tablet count in the blister pack.
- The sponsor agreed to check whether a DMF is available for the tablet coating colorant and to provide a Letter of Authorization to that DMF.

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/s/

David T. Lin
7/26/01 09:27:42 AM
CHEMIST
Request for CMC info.

Teleconference Minutes

Date: June 20, 2001 **Time:** **Location:** Parklawn; 17B-31

NDA 4-782/SE2-115 **Drug:** Premarin Tablets

Indication: VMS

Type of Meeting: Chemistry Information Request

External Constituent: Wyeth-Ayerst

Meeting Chair: David Lin, Ph.D.

Meeting Recorder: David Lin, Ph.D.

FDA Attendees:
David Lin, Ph.D.-Chemist, Division of New Drug Chemistry II (DNDCII) @ Division of Reproductive and Urologic Drug Products (HFD-580)

External Participants:
Dr. Nirdosh Jagota, Worldwide Regulatory Affairs

Purpose of the Meeting:
To request additional information on the proposed container/closure system for the drug product tablets, mock-ups of the container and carton labels, and clarification of release testing.

Decisions Made:
- The sponsor agreed to verify if the proposed container/closure system for the 0.45 mg strength tablet is the same as for the approved strength tablets.
- The sponsor agreed to modify the drug product manufacturing section to indicate that release testing of the Premarin Tablets is performed after polishing and branding.
- The sponsor agreed to provide mock-ups of the container and carton labels.

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

/s/

David T. Lin
7/26/01 09:23:43 AM
CHEMIST
Request for CMC info.

Division of Reproductive and Urologic Drug Products

ADMINISTRATIVE REVIEW OF APPLICATION

Application Number: N-4782/S-115

Name of Drug: Premarin® (conjugated estrogens) Tablets, 0.45 mg

Sponsor: Wyeth-Ayerst Laboratories, Inc.

Material Reviewed

Submission Date: July 31, 2000

Receipt Date: July 31, 2000

Filing Date: September 29, 2000

User-fee Goal Date(s): May 31, 2001; July 31, 2001

Proposed indication: VMS, VVA

Other Background Information:

Review

PART I: OVERALL FORMATTING[a]

	Y	N	**COMMENTS (list volume & page numbers)**
1. Cover Letter (original signature)	X		Volume 1, page 1
2. Form FDA 356h (original signature)	X		Volume 1
a. Reference to DMF(s) & Other Applications	X		N/A
3. Patent information & certification	X		Volume 1, page 20-21
4. Debarment certification (note: must have a definitive statement)	X		Volume 1, page 23
5. Financial disclosure	X		Volume 1, page 26
6. Comprehensive Index	X		Volume 1, page 7
7. Pagination	X		throughout
8. Summary Volume	X		Volume 3
9. Review Volumes	X		Volumes 3-65
10. Labeling (PI, container, & carton labels)	X		Volumes 2 and 3
a. unannotated PI	X		Volume 2, page 2
b. annotated PI	X		Volume 3, page 1
c. immediate container	X		Volume 2, page 25
d. carton	X		Volume 2, page 25

e. foreign labeling (English translation)		X	N/A
11. Foreign marketing History		X	N/A
12. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		electronic file system
13. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		electronic file system

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b]

	Y	N	COMMENTS (list volume & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		Volume 3, page 150
2. Summary of Each Technical Section	X		
a. Chemistry, Manufacturing, & Controls (CMC)	X		Volume 3, page 25
b. Nonclinical Pharmacology/Toxicology		X	N/A (already approved at higher dosages)
c. Human Pharmacokinetic & Bioavailability	X		Volume 3, page 49
d. Microbiology		X	N/A (tablet form)
e. Clinical Data & Results of Statistical Analysis	X		Volume 3, page 50
3. Discussion of Benefit/Risk Relationship & Proposed Post-marketing Studies	X		Volume 3, page 150
4. Summary of Safety		X	N/A only one study submitted
5. Summary of Efficacy		X	N/A only one study submitted

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STTISTICAL SECTIONS[c]

	Y	N	COMMENTS (list volume & page numbers)
1. List of Investigators	X		Volume 1, page 27
2. Controlled Clinical Studies	X		
a. Table of all studies	X		Volume 21, page 4
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		Volume 48, page 10
c. Optional overall summary &		X	N/A see Volume 47, page 296

evaluation of data from controlled clinical studies			
3. Integrated Summary of Efficacy (ISE)		X	N/A one study performed
4. Integrated Summary of Safety (ISS)		X	N/A one study performed
5. Drug Abuse & Overdosage Information	X		Volume 47, page 297
6. Integrated Summary of Benefits & Risks of the Drug	X		Volume 47, page 310
7. Gender/Race/Age Safety & Efficacy Analysis Studies		X	

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS

	Y	N	**COMMENTS (list volume & page numbers)**
1. Written Documentation Regarding Drug Use in the Pediatric Population		X	Waiver request, Volume 1, page 43
2. Diskettes	X		
a. Proposed unannotated labeling in MS WORD 8.0	X		
b. Stability data in SAS data set format		X	
c. Efficacy data in SAS data set format		X	
d. Biopharmacological information & study summaries in MS WORD 8.0		X	requested
e. Animal tumorigenicity study data in SAS data set format		X	N/A drug approved in higher strengths
3. User-fee payment receipt	X		Volume 1, page 25

Y=Yes (Present), N=No (Absent)

a"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

b"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

c"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

Additional Comments:

Conclusions
Fileable

_____
Name
Regulatory Health Project Manager

cc:
Original NDA 4-782/S-115
HFD-580/Div. Files
HFD-580/CSO/D.Moore/T.Rumble
HFD-580/SAllen/MMann/SSlaughter/MRhee/AJordan/AParekh/LKammerman
draft:
r/d initials
final: October 17, 2000

ADMINISTRATIVE REVIEW

Revised 3/22/00

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/s/

Diane V. Moore
7/10/01 04:36:31 PM
CSO

Terri F. Rumble
7/16/01 05:00:10 PM
CSO

Meeting Minutes

Date: June 26, 2001 **Time:** 2:30 - 2:45 PM **Location:** Parklawn; Room 17B-43

NDA: 4-782/S-115 **Drug:** Premarin (conjugated estrogens tablets, USP), 0.45 mg

Type of Meeting: 11 month Status

Sponsor: Wyeth-Ayerst Laboratories, Inc.

Indication: relief of vasomotor symptoms (VMS) and vulvar and vaginal atrophy (VVA) associated with the menopause

Meeting Chair: Dr. Daniel Shames

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Dan Shames, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D.- Medical Team Leader, (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, (DRUDP; HFD-580)
Diane Moore - Regulatory Project Manager (DRUDP; HFD-580)
David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II)@ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Background: This is an efficacy supplement for the 0.45 mg dose of Premarin. The 12-month goal date is July 31, 2001.

Meeting Objective: To discuss the status of the reviews and labeling for supplement 115.

Decisions:
- Clinical
  - drafted review with recommendation for approval currently under secondary review; labeling has been updated on the division server file
  - The Team Leader will omit comments to the CMC section in the TL memo because the CMC review may be delayed because of the GMP issue
- Chemistry
  - Review pending; awaiting Compliance recommendation regarding the acceptability of the manufacturing sites
  - The reviewer requested confirmation from the sponsor last week on the packaging configuration

- Biopharmaceutics
  - Review pending; labeling comments pending
  - *in vitro* dissolution data for clinical and to-be-marketed formulations were received from the sponsor; the submitted data justify the similarity between clinical and the to-be-marketed formulations; the Biopharm briefing is to be scheduled soon
- the Division will proceed with finalizing labeling recommendations on the division server file; labeling comments will be sent to the sponsor in 1-2 weeks
- all reviews are due to Dr. Slaughter by July 10, 2001

Action Items:

Item:	**Responsible Person:**	**Due Date:**

Signature, recorder

Signature, Chair

drafted: dm/7.3.01/N4782S115SM62601.doc
Concurrence:
T.Rumble 7.5.01/D.Shames 7.9.01/T.van der Vlugt 7.10.01/S.Slaughter 7.12.01
D.Lin, J.Lau 7/17/01

No response was received from A. Parekh

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/s/

Diane V. Moore
7/20/01 12:43:56 PM

Daniel A. Shames
7/24/01 10:09:45 AM

Meeting Minutes

Date: May 22, 2001 **Time:** 10:30 – 10:50 AM **Location:** Parklawn; Room 17B-45

NDA: 4-782/S-115 **Drug Name:** Premarin (conjugated estrogens tablets, USP) 0.45 mg

Type of Meeting: Status/Labeling

External Constituent: Wyeth-Ayerst Research

Meeting Chair: Dr. Daniel Shames

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Daniel Shames, M.D. – Deputy Director, DRUDP (HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Meeting Objective:
To discuss the status of the reviews and the labeling for Supplement-115 for the new 0.45 mg dose for the treatment of moderate-to-severe vasomotor symptoms (VMS) associated with the menopause and the treatment of vulvar and vaginal atrophy (VVA).

Background: The date to circulate the action package will be July 17, 2001. Primary reviews should be provided to the Team Leaders by July 3, 2001.

Decisions:
- Clinical
  - review pending; labeling comments have been added to the labeling on the Division "N" drive
- DSI
  - no inspection was requested because this product has been approved at higher doses
- Statistics
  - review completed
- Chemistry, Manufacturing and Quality Control
  - review pending
  - the storage statement needs to be revised; comments will be included on the labeling on the Division "N" drive
  - the recommendation from the manufacturing site inspection is pending

- Pharmacology
  - there are no labeling comments to include in the draft label per the pharmacology reviewer
- Clinical Pharmacology and Biopharmaceutics
  - review pending
  - the individual dissolution data was requested from the sponsor on April 27, 2001; the data submitted was not in a suitable format; the data will be requested again in a more functional format
  - labeling comments will be added to the labeling on the Division "N" drive
- Labeling
  - the EES issue will most likely not be resolved by the action date for this application; therefore, labeling comments will not be conveyed to the sponsor prior to the action date; comments will be included in the action letter; no DDMAC review will be included for this review cycle since this application will not be approved
- Regulatory
  - there will be no OPDRA safety meeting for this review cycle since this application will not be approved
  - in lieu of a June status meeting, a reminder e-mail will be sent to remind the reviewers to finalize their reviews and send copies to the Project Manager and the Clinical Team Leader

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• request *in vitro* dissolution data from sponsor	Ms. Moore	1-day
• Send e-mail to reviewers to finalize reviews	Ms. Moore	July 3, 2001

_____
Signature, minutes preparer

Post meeting addendum: On May 9, 2001, in response to the April 27, 2001 agency request, the sponsor submitted an amendment to Supplement S-115 providing *in vitro* data; however, the data was not provided in a suitable format for substantiating no difference between the clinical batches and the to-be-marketed batches. The individual *in vitro* dissolution data that were presented were grouped in three sampling time-points rather than each tablet's individual dissolution data at the three sampling time-points. On the morning of May 22, 2001, the clinical pharmacology and biopharmaceutics reviewer and the project manager informed Dr. Joseph Sonk, at Wyeth-Ayerst that the data needed to be submitted for each tablet at 2 hour, 5 hour and 8 hour time-points with the average, CV and range plotted. The sponsor agreed to send the information in the new format by the next day. The afternoon of May 22, 2001, Dr. Nirdash Jagota, of Wyeth-Ayerst contacted the biopharmacetics reviewer and project manager to inform them that the submission would be delayed until May 24, 2001. The reviewer acknowledged the request and agreed to the delay.
The sponsor submitted the requested data on May 24, 2001.

drafted: dm/5.22.01/N4782S115SM42601

Concurrence:

T.Rumble, J.Lau 5.24.01/S.Slaughter 5.25.01/D.Lin 5.30.01/T.van der Vlugt 7.2.01
D.Shames 7.9.01

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/s/

Diane V. Moore
7/10/01 10:03:04 AM

Daniel A. Shames
7/13/01 01:38:07 PM

WYETH-AYERST RESEARCH

ORIGINAL

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

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

June 29, 2001

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

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

NDA SUPPLEMENT
SE2 115 (S-)

Dear Dr. Allen:

Reference is made to NDA No. 04-782/S-115 for Premarin® (conjugated estrogens tablets, USP). Reference is also made to the two telephone conversations of June 20 and 22, 2001 between Wyeth-Ayerst (Dr. Nirdosh Jagota and Susan Wilson, respectively) and FDA (Dr. David Lin).

Dr. Lin had several comments, which were in reference to our Prior Approval Supplement S-115 for Premarin® (conjugated estrogens tablets, USP). This Supplemental Application (S-115) provided for a new low dose of Premarin Tablets (0.45mg). The verbal comments provided by the FDA pertained to the container/closure system, release testing before polishing and branding, mock-up labels and cartons, and a Drug Master File authorization letter. Wyeth-Ayerst has provided responses to each of Dr. Lin's comments in the attachments.

To facilitate review, this submission is organized by the telephone contact date and sequential order of comments. The FDA comment is provided in boldface type followed by the Wyeth-Ayerst response in standard type.

If you have any questions regarding this submission, please contact the undersigned at (610) 902-3743 or Dr. Karel Bernady at (610) 902-3760.

Sincerely,

WYETH-AYERST LABORATORIES

Karel A. Bernady for N.J.

Nirdosh Jagota, Ph.D.
Director
Worldwide Regulatory Affairs

Attachments
Desk Copy: Diane Moore
Dr. David Lin
U:\Premarin\04782\Clt Allen 062901.doc

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

WYETH-AYERST RESEARCH

DESK COPY

June 12, 2001

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

Susan Allen, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Allen:

Reference is made to NDA No. 04-782/S-115 for Premarin® (conjugated estrogens tablets, USP) submitted to DRUDP on July 31, 2000.

Further reference is made to a request from Ms. Diane Moore on June 7, 2001 for specific information from the Women's HOPE Study (Protocol 0713D2-309-US) pertaining to treatment group assignments for 14 patients listed below.

Our response follows:

Patient Number	Treatment Group
30907-0012	0.45mg
30907-0016	0.625mg
30907-0029	0.625mg
30907-0030	0.45mg
30709-0039	0.45mg
30918-0030	0.625mg
30918-0087	0.45mg
30923-0026	0.30mg
30923-0046	0.45mg
30925-0026	0.625mg
30932-0011	0.625mg
30936-0006	0.625mg
30936-0040	0.625mg
30958-0024	0.625mg

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

Sincerely,

WYETH-AYERST LABORATORIES

Kathryn Labash

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

Desk copy: Ms. Diane Moore, Regulatory Project Manager

WYETH-AYERST RESEARCH

CN 8299 • PHILADELPHIA, PA 19101-8299 • (610) 902-5700 • FAX (610) 962-5973
JOSEPH_SONKI@WYETH.COM

Division of American Home Products Corporation

JOSEPH SONKI, PhD
Assistant Vice President
Worldwide Regulatory Affairs

ORIGINAL

June 5, 2001

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

Susan Allen, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA SUPP AMEND
3(2-115

Dear Dr. Allen:

Reference is made to NDA No. 04-782/S-115 for Premarin® (conjugated estrogens tablets, USP) submitted to DRUDP on July 31, 2000.

Further reference is made to a request from Ms. Diane Moore on May 30, 2001 for specific information from the Women's HOPE Study (Protocol 0713D2-309-US) pertaining to mammogram results, treatment group assignments and post-database cutoff data findings as follows:

1. The treatment group assignments for patients: 30918-0044 and 30936-0017.
2. Screening mammogram results for patients: 30918-0044, 30936-0017, 30919-0112, 30936-0033 and 30960-0012.
3. Submission of any additional post-database cutoff data findings.

Our responses follow.

1. The treatment group assignment for patient: 30918-0044 is Group H, placebo and 30936-0017 is Group E, 0.45mg CE / 1.5mg MPA.

2. The following patient information is enclosed as Attachments 1-5.

30918-0044	Attachment 1	Screening mammogram (12/23/96)
30936-0017	Attachment 2	Screening mammogram (05/06/97)
30919-0112	Attachment 3	Screening mammogram (09/03/98)
30936-0033	Attachment 4	Screening mammogram (03/06/98)
30960-0012	Attachment 5	Screening mammogram (06/12/96)

3. There are no new data findings from the post-database cutoff for Premarin alone subsequent to the submission of March 29, 2001. For the convenience of the reviewer, we are resubmitting the enclosed report (Volume 1) entitled:

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

as an amendment to NDA. No 04-782/S-115 as Attachment 6.

These findings do not change the safety and efficacy conclusion of Protocol 0713D2-309 (The HOPE Study) YEAR-1, nor do they significantly alter the labeling. The enclosed report provides additional information, which was obtained after the database was locked (December 29, 1999) for the 1-Year Interim Report (GMR-38605). A summary of the findings post-database cutoff is provided in Table 1 of this report. It should be noted that the title of Table 1 should read: SUMMARY OF POST-DATABASE CUTOFF FINDINGS EVALUATED FOR YEAR 1 PATIENTS in sNDA 20-527/S-017 **and sNDA 04-782/S-115** BASED ON GMR-38605. The bold lettering represents an inadvertent omission in the title. ***As a result of these findings, treatment emergent adverse events, has been revised accordingly and is provided as Table 2 in this report.*** Details of all findings for each type of data from year 1 are included in the enclosed report under Supportive Tables.

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

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

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

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

Sincerely,

WYETH-AYERST LABORATORIES

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Desk copy: Ms. Diane Moore

WYETH-AYERST RESEARCH

U.S. REGULATORY AFFAIRS

NDA SUPP AMEND

ORIGINAL

May 24, 2001

NDA 04-782/S-115
Premarin® (conjugated estrogens tablets, USP)

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

Dear Dr. Allen:

Reference is made to NDA 04-782/S-115 for Premarin (conjugated estrogens tablets, USP).

In response to Dr. Johnny Lau telephone request on May 22, 2001, Wyeth-Ayerst is re-submitting the data which was previously submitted in the May 9, 2001 correspondence to the Agency. The re-submitted data supplied in this correspondence has been formatted to match the data supplied by Wyeth-Ayerst in the February 28, 2001 submission. Please note that the data submitted in today's correspondence only differs in format from the previously submitted data.

As previously submitted on May 9, 2001, this submission consists of individual tablet dissolution data for clinical and proposed commercial lots of Premarin 0.45mg tablets along with descriptive statistics. The following are enclosed with this submission:

- Dissolution data on registration lots A00D001, A00D002, A00D003 submitted in NDA 04-782/S-115 for Premarin Tablets 0.45 mg using the USP 24 Method (3256-178) and the USP 24 Method with [ ] (L20744-005) under the following conditions:

  [ ] Bottles @ 25° C/60% RH for 9 months
  [ ] Bottles @ 25° C/60% RH for 12 months
  PVC Blisters @ 25° C/60% RH for 9 months
  PVC Blisters @ 25° C/60% RH for 12 months

- Dissolution data on clinical lots 3TEL and 1997B0091 submitted in NDA 04-782/S-115 for Premarin Tablets 0.45 mg using the USP 24 Method (3256-178) and the USP 24 Method with

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

P.O. BOX 8299 PHILADELPHIA, PA 19101-8299 • (610) 902-3710 • FAX (610) 902-3971

Meeting Minutes

Date: April 26, 2001 **Time**: 11:00 – 11:15 AM **Location:** Parklawn; Room 17B-45

NDA: 4-782/S-115 **Drug Name**: Premarin (conjugated estrogens tablets, USP) 0.45 mg

Type of Meeting: Status/Labeling

External Constituent: Wyeth-Ayerst Research

Meeting Chair: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Meeting Objective:
To discuss the status of the reviews and the labeling for Supplement-115 for the new 0.45 mg dose for the treatment of moderate-to-severe vasomotor symptoms (VMS) associated with the menopause and the treatment of vulvar and vaginal atrophy (VVA).

Background: The date to circulate the action package will be July 17, 2001. Primary reviews should be provided to the Team Leaders by July 3, 2001.

Discussion Items:
- Clinical
  - review pending
- Statistics
  - review completed
- Chemistry, Manufacturing and Quality Control
  - review pending
  - EES recommendation pending
  - the storage statement needs to be revised
  - the sponsor submitted a correspondence to the Agency on March 9, 2001; a meeting with the Center Director was held on April 25, 2001 to discuss outstanding dissolution issues
  - the recommendation from the manufacturing site inspection is pending
- Clinical Pharmacology and Biopharmaceutics
  - review pending

- because there is a difference in the color of the formulation studied in the clinical study and the to-be-marketed formulation, it will be necessary to request individual dissolution data from the sponsor for both batches at release for the 0.45 mg conjugated estrogens tablets

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• request *in vitro* dissolution date from sponsor	Ms. Moore	1-week

_____
Signature, minutes preparer

Addendum to Minutes:

- On April 27, 2001, the Project Manager conveyed the request for individual *in vitro* dissolution data plus descriptive statistics (mean and range, etc.) for the clinical batches and the to-be-marketed batches at release for the 0.45 mg conjugated estrogens tablets to substantiate the color differences. It was requested that the information be submitted within two weeks of the request.
- At a January 2001 retreat with the Division Director, Deputy Director and Chief, Project Management Staff, the goal dates of the pending applications were discussed and revised so as to arrange an improved workload priority list. During this meeting, it was decided that the goal date for this application should be moved from the primary goal date (May 31, 2001) to the secondary goal date (July 31, 2001). The goal date was officially moved at the Division retreat on February 13, 2001. Consequently, the due date for circulating the action package is July 17, 2001.

drafted: dm/4.27.01/N4782S115SM42601

Concurrence:
T.Rumble 5.3.01/J.Lau 5.4.01/T.van der Vlugt 5. 7.01/D.Lin 5.10.01/S.Slaughter 5.11.01

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

/s/

Diane V. Moore
5/21/01 05:51:30 PM

Shelley Slaughter
5/22/01 04:05:48 PM

WYETH-AYERST RESEARCH

May 15, 2001

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

Susan Allen, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Allen:

Reference is made to NDA No. 04-782/S115 for Premarin® (conjugated estrogens tablets, USP) submitted to DRUDP on July 31, 2000.

As requested during a discussion with Ms. Moore on May 8th, please find the attached safety report for this submission. The summary information from the report has been faxed to the Division this day.

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

Sincerely,

WYETH-AYERST LABORATORIES

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

REVIEWS COMPLETED
ACTION
☐ LETTER ☐ E.A.L. ☐ MEMO
CSO INITIALS DATE

Desk copy: Ms. Diane Moore

JSS:laf\017

WYETH-AYERST RESEARCH ORIGINAL

U.S. REGULATORY AFFAIRS

May 9, 2001

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

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

NDA SUPP AMEND

Dear Dr. Allen:

Reference is made to NDA No. 04-782/S-115 for Premarin (conjugated estrogens tablets, USP).

In response to Dr. Johnny Lau and Diane Moore's request by telephone on April 27, 2001 for individual tablet dissolution data for clinical and proposed commercial lots of Premarin 0.45mg tablets along with descriptive statistics, the following are enclosed with this submission:

- Dissolution data on registration lots A00D001, A00D002, A00D003 submitted in NDA 04-782/S-115 for Premarin Tablets 0.45 mg using the USP 24 Method (3256-178) and the USP 24 Method with [ ] (L20744-005) under the following conditions:

  [ ] Bottles @ 25° C/60% RH for 9 months
  [ ] Bottles @ 25° C/60% RH for 12 months
  PVC Blisters @ 25° C/60% RH for 9 months
  PVC Blisters @ 25° C/60% RH for 12 months

- Dissolution data on clinical lots 3TEL and 1997B0091 submitted in NDA 04-782/S-115 for Premarin Tablets 0.45 mg using the USP 24 Method (3256-178) and the USP 24 Method with [ ] (L20744-005). The clinical lots were stored in [ ]

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

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

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

Sincerely,
WYETH-AYERST LABORATORIES

Nirdosh Jagota, Ph.D.
Director
Worldwide Regulatory Affairs

Attachments

Desk Copy: Diane Moore

U:\Premarin\04782 Cli 050901.doc

Meeting Minutes

Date: March 27, 2001 **Time:** 2:30 – 2:45 PM **Location:** Parklawn; Room 17 B-43

NDA: 4-782/S-115 **Drug Name:** Premarin (conjugated estrogens, USP) tablets, 0.45 mg

Type of Meeting: 8-month status meeting

Sponsor: Wyeth-Ayerst Research

Meeting Chair: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Shelley Slaughter, M.D., Ph.D. – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H. – Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, DRUDP (HFD-580)
David Lin, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Meeting Objective:
To discuss the status of Supplement-115 for the new 0.45 mg dose for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause and the treatment of vulvar and vaginal atrophy.

Background: Primary reviews should be provided to the Team Leaders by May 14, 2001.

Decisions reached:
- Pharmacology
  - no formal review needed; a memorandum will be submitted to DFS
- Clinical
  - review pending
  - EES recommendation pending
- Statistics
  - review pending
- Chemistry, Manufacturing and Quality Control
  - review pending
- Clinical Pharmacology and Biopharmaceutics
  - review pending
  - dissolution specifications can be bracketed between the 0.3 mg and 0.625 mg doses
- Regulatory
  - a copy of the Clinical Pharmacology and Biopharmaceutics review will be provided for the Medical Team Leader when available

Action Items:	Responsible Person:	Due Date:
• provide B/P review to Medical Team Leader	Ms. Moore	when available

Signature, minutes preparer

Concurrence, Chair

drafted dm/2.3.01/N4782S115SM32701

Concurrence:
J.Best, J.Lau, D.Lin 4.2.01/S.Slaughter 4.3.01
No response received from T.van der Vlugt

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

/s/

Diane V. Moore
4/19/01 01:14:41 PM

Shelley Slaughter
4/23/01 01:15:25 PM

WYETH-AYERST RESEARCH

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

WORLDWIDE REGULATORY AFFAIRS

ORIGINAL

Division of American Home Products Corporation

NDA SUPP AMEND

April 2, 2001

S e 2 - 11 5 PMN

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

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

Dear Dr. Allen:

Reference is made to NDA No. 04-782/S-115 for PREMARIN (conjugated estrogens tablets, USP) submitted to DRUDP on July 31, 2000.

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

On March 26, 2001, I contacted Ms. Diane Moore to inform her of additional database findings from Protocol 0713D2-309-US that were obtained after the database was locked (December 23, 1999) for the 1-Year Interim Report (GMR-38605) and therefore not previously submitted as part of NDA No. 04-782/S-115. The purpose of my call was to inform her of this information and seek advice on the appropriate timing for submission of this information to the Agency as an amendment to the sNDA. I informed Ms. Moore that, (1) the new findings are the result of information from Clinical Research quality assurance reviews, routine data cleanup activities resulting from these reviews, site visits by Clinical Scientists and Regional Clinical Associates, resolution of queries issued by the Clinical Data Management department, and (2) the findings have been carefully evaluated and do not change the safety and efficacy conclusions of Protocol 0713D2-309 (The HOPE Study) Year-1, nor do they significantly alter the labeling.

Ms. Moore confirmed with the Medical Officer, Dr. Van Der Vlugt, that this information should be submitted to the Agency as an amendment to NDA 04-782/S-115 as soon as possible.

The enclosed report (Volume 1) entitled:

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

is being submitted as an amendment to NDA No. 04-782/S-115.

NDA No. 04-782/S-115 submitted on July 31, 2000, provided final data for the basic study patients as an Interim Report for study 0713D2-309-US. The enclosed report provides additional information, which was obtained after the database was locked (December 29, 1999) for the 1-Year Interim Report (GMR-38605). A summary of the findings post-database cutoff is provided in Table 1 of this report. As a result of these findings, Table 3 – treatment emergent adverse events - of the proposed labeling submitted with NDA 04-782/S-115 will be revised to reflect the changes in TEAEs for the single-entity groups and placebo as identified in bold in Table 2 of this report. Details of all findings for each type of data from year 1 are included in the enclosed report under Supportive Tables.

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

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

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

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

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

Desk Copy: Ms. Diane Moore

JDN:lad\808

Meeting Minutes

Date: January 30, 2001 **Time**: 3:00 – 3:15 PM **Location:** Parklawn; Room 17 B-43

NDA: 4-782/S-115 **Drug Name:** Premarin (conjugated estrogens, USP) tablets, 0.45 mg

Type of Meeting: 6-month status meeting

Sponsor: Wyeth-Ayerst Research

Meeting Chair: Dr. Dan Shames

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Dan Shames, M.D., - Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., M.P.H. – Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
David Lin, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Lisa Kammerman, Ph.D. – Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objective:
To discuss the status of Supplement-115 for the new 0.45 mg dose for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause and the treatment of vulvar and vaginal atrophy.

Background: Primary reviews should be provided to the Team Leaders by May 14, 2001.

Decisions reached:
- Pharmacology
  - since conjugated equine estrogens (CEE) has been approved in higher doses, Pharmacology has no objections to approval; a memorandum to the supplemental NDA will be drafted to that effect
- Clinical
  - review pending
- Statistics
  - review pending
- DSI
  - a DSI inspection was not requested because the drug substance is an approved drug substance for the intended indications; no significant differences in study demographics and outcomes were observed between the individual participating study centers; the one investigator financial disclosure that was questioned involved a center with a small number of enrolled subjects for which a DSI inspection was not warranted
- Financial Disclosure

- review pending
- Chemistry, Manufacturing and Quality Control
  - review pending
  - a supplement to revise the dissolution specifications to add [redacted] has been submitted (S-116)
- Clinical Pharmacology and Biopharmaceutics
  - review pending
- Regulatory
  - a copy of the labeling in WORD 97 is on the N: drive for sharing labeling comments within the team
  - a requested PK data and annotated labeling from the sponsor has been requested

Action Items:	**Responsible Person:**	**Due Date:**
• none		

_____ _____

Signature, minutes preparer Concurrence, Chair

drafted dm/2.3.01/N4782S115SM2301

Concurrence:

T.Rumble, T.van der Vlugt, J.Lau 2.5.01/DShames 2.6.01/S.Slaughter 2.13.01/D.Lin 2.22.01
A.Parekh 2.27.01

Response not received from Lisa Kammerman

/s/

Diane V. Moore
3/15/01 09:43:27 PM

Daniel A. Shames
3/19/01 12:36:06 PM

WYETH-AYERST RESEARCH

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

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

ORIGINAL

March 14, 2001

NDA No. 04-782/S-115
Premarin® (conjugated estrogens tablets, USP)
NDA SUPP AMEND
SC-2-115-BC

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

Dear Dr. Allen:

Reference is made to NDA No. 04-782/S-115 for PREMARIN (conjugated estrogens tablets, USP) 0.45 mg submitted to the FDA on July 31, 2000.

The following reports are being submitted as an amendment to NDA 04-782/S-115:

- Method No. L20744-005: Dissolution of Conjugated Estrogens in Premarin Tablets Using [ ]
- GTR-33641: Suitability of Method 3256-178 for the Dissolution of Conjugated Estrogens in Premarin Tablets
- RPT-41259: Suitability of Method L20744-005 for Determining the Dissolution of Conjugated Estrogens from Premarin Tablets Using [ ]

The corresponding pages from NDA No. 04-782/S-115, which reference the above reports, have also been updated and are enclosed:

Item 4: Chemistry Section

4.3.5 Proposed Regulatory Specifications
4.3.5.1 Dosage Form

4.3.6 Detailed Description of Each Method of Analysis
4.3.6.1 Dosage Form

4.3.7 Information Supporting the Suitability of the Methodology for the Drug Product

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

For your convenience a copy of the Table of Contents from NDA No. 04-784/S-115 is enclosed as a reference.

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

JDN:lad\799

WYETH-AYERST RESEARCH

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

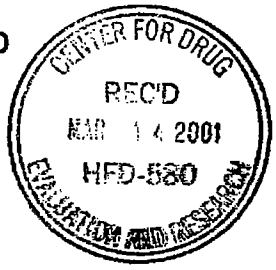
Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

ORIGINAL

March 13, 2001

NDA SUPP AMEND



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

SE2 115 (PL)

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

Dear Dr. Allen:

Reference is made to NDA No. 04-782/S-115 for PREMARIN (conjugated estrogens tablets, USP) 0.45 mg submitted to the FDA on July 31, 2000.

Further reference is made to a recent communication on March 6, 2001 between Dr. Nirdosh Jagota of Wyeth-Ayerst and Ms. Diane Moore and Dr. David Lin regarding Wyeth-Ayerst's commitment to submit additional stability data to support the expiration dating for PREMARIN 0.45 mg to DRUDP by March 13, 2001.

The following 12-month stability report is being submitted as an amendment to NDA 04-782/S-115:

Volume 1

- RPT -39219: Report of Twelve Months Stability Data for PREMARIN 0.45 mg Tablets in [ ] Bottles and PVC Blisters (including statistical analysis-SRN01-017).

The report summarizes 12-months of 25°C/60%RH, 30°C/60%RH, 30°C/70%RH (blisters only) stability data, and 6 month stability data stored at 40°C/75%RH on 3 batches of PREMARIN 0.45mg. Dissolution testing utilizing [ ] was instituted at the 9-month time point; therefore, data with and without [ ] are included for batches at 9-month and 12-month time points. Dissolution testing at time points after 12 months will be done with the use of [ ] only. Six month samples stored at 40°C/75% RH were also tested with [ ]

demonstrated period of use of 5 years for all marketed strengths of PREMARIN tablets, an expiration dating period of 24 months at room temperature is proposed for PREMARIN 0.45 mg tablets in[ ] bottles with [ ] or PVC blisters.

Also enclosed with this submission as amendments to NDA 04-782/S-115 are the following reports:

Volume 2

- Updated specification pages (5 pages total) to relevant sections of NDA 04,782/S-115:

3.2.1.1.6	Specifications and Analytical Methods
4.1.4.6	Specifications and Analytical Methods for the Drug Product
4.1.4.7.2	Stability Commitment, Expiry Date, and Stability Protocol

- Method No. L20744-005 (Wyeth-Ayerst Research Version): Dissolution of Conjugated Estrogens in Premarin Tablets Using [ ]
- Method No. L20744-005 (Quality Assurance Version): Dissolution of Conjugated Estrogens in Premarin Tablets Using [ ]
- GTR-33641: Suitability of Method 3256-178 for the Dissolution of Conjugated Estrogens in Premarin Tablets.
- RPT-41259: Suitability of Method L20744-005 for Determining the Dissolution of Conjugated Estrogens from Premarin Tablets Using [ ]

There are two versions of Method No. L20744-005 provided. The Wyeth-Ayerst Research version of this method has been used in testing NDA stability samples (see RPT-39219); the Quality Assurance version will be used to test market product and market product stability samples. The two versions are identical with the exception that the Quality Assurance version requires deaeration of the dissolution medium (as requested by FDA).

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

JDN:lad\798

Desk Copy: Dr. David Lin

WYETH-AYERST RESEARCH

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

WORLDWIDE REGULATORY AFFAIRS

Division of American Home Products Corporation

ORIGINAL

February 2, 2001

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

NDA SUPP AMEND

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

SC 2-115-BM

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

Dear Dr. Allen:

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

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

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

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

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

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

JDN:lad\780

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Law

WYETH-AYERST RESEARCH

BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

DUPLICATE

January 11, 2001

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

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

NEW CORRESP

Dear Dr. Allen:

Reference is made to NDA No. 04-782/S-115 for Premarin (conjugated estrogens tablets, USP).

In response to Ms. Diane Moore's request by telephone on October 17, 2000 for dissolution data on the clinical lots and registration lots submitted in NDA No. 04-782/S-115 for Premarin Tablets 0.45 mg, enclosed with this submission are the following:

- Dissolution data on registration lots A00D001, A00D002, A00D003 submitted in NDA 04-782/S-115 for Premarin Tablets 0.45 mg using the USP 24 Method (3256-178) and the USP 24 Method with [ ] (L20744-005) under the following conditions:

  [ ] Bottles @ 25° C/60% RH for 9 months
  PVC Blisters @ 25° C/60% RH for 9 months
  [ ] Bottles @ 40° C/75% RH for 6 months
  PVC Blisters @ 40° C/75% RH for 6 months
  [ ] Bottles @ 30° C/ 60% RH for 9 months
  PVC Blisters @ 30° C/ 60% RH for 9 months
  PVC Blisters @ 30° C/ 70% RH for 9 months

- Dissolution data on clinical lots 3TEL and 1997B0091 submitted in NDA 04-782/S-115 for Premarin Tablets 0.45 mg using the USP 24 Method (3256-178) and the USP 24 Method with [ ] (L20744-005). The clinical lots were stored in [ ] [ ]

As noted in the attached report, dissolution data provided for the registration lots of Premarin 0.45 mg tablets stored for 9 months at 25°C/60% RH met USP<724> acceptance criteria when either the USP 24 Method or the USP 24 Method with [ ] were

used. Samples from these same lots exposed to accelerated storage (40°C/75% RH) for 6 months did not meet USP<724> acceptance criteria when the USP 24 Method was used and met these acceptance criteria (at USP<724> Levels 1, 2 or 3) when the USP 24 Method with [ ] was used. It should be noted that although samples stored at 40°C/75% RH and tested by the USP 24 Method (without [ ]) did not meet USP <724> acceptance criteria, testing performed on samples stored for 9 months at the recommended ICH "backup" condition of 30°C/60% RH met acceptance criteria with this method.

As requested, the two clinical lots of Premarin 0.45 mg tablets were tested using the USP 24 Method as well as the USP 24 Method with [ ] When tested using the USP 24 Method, one of these lots did not meet USP<724> acceptance criteria. Both lots, however, met these criteria when tested using the USP 24 Method with [ ]

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman
Associate Director
Worldwide Regulatory Affairs

ORIGINAL

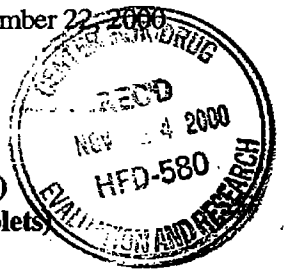
WYETH-AYERST RESEARCH

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

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

November 22, 2000



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

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

General Correspondence
(Financial Disclosure)

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

BM
NDA SUPP AMEND
SE2-115

Dear Dr. Allen:

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

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

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

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

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

LTH-1019
LTH-1019

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

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

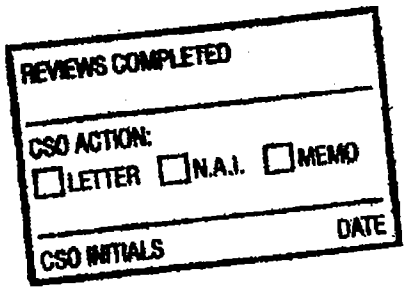
Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman, Manager
Worldwide Regulatory Affairs

JDN:lad\761



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WORLDWIDE REGULATORY AFFAIRS

Division of American Home Products Corporation

ORIGINAL

November 30, 2000

NDA No. 04-782/S-115
Premarin® (conjugated estrogens tablets, USP) **4 Month Safety Update**

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

NDA SUPP AMEND
SC-2-115-SU1

Dear Dr. Allen:

Reference is made to our NDA No. 04-782/S-115 previously submitted to your administration on July 31, 2000. This sNDA supports the use of Premarin 0.45mg for the treatment of moderate to severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy.

The purpose of this submission is to provide the 4-Month Safety Update for the above referenced new drug application. This submission contains Item 9, 4-Month Safety Update with supportive tables and four appendices. The Appendices contain the following information:

Appendix 1: Listing of study events by patient

Appendix 2: Summary tabulation of treatment-emergent study events by severity and drug relationship, including identification of patients

Appendix 3: Listing by investigator and patient of reasons for discontinuation

Appendix 4: Patient narratives

The above is provided as an electronic file. The electronic items are provided per the FDA "Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs" issued January 1999. These items are provided on 1 CD-ROM. In addition to the copy the Division is receiving, one copy was submitted to the FDA/CDER Central Electronic File Room for uploading onto the FDA network. The single CD contains approximately 3 Megabytes.

If you have any questions regarding this submission, please contact me at (610) 902-3749.

Sincerely,

WYETH-AYERST RESEARCH

Jennifer D. Norman

Jennifer D. Norman, Manager
Worldwide Regulatory Affairs

JDN:lad\762

Desk Copy:
Mrs. Diane Moore, Project Manager

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

WYETH-AYERST RESEARCH

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

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

ORIGINAL

October 24, 2000

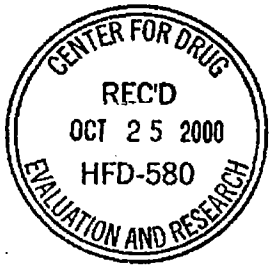
NDA No. 04-782/S-115
Premarin (conjugated estrogens tablets, USP)

[redacted]
Prempro (conjugated estrogens/medroxyprogesterone acetate tablets)
Premphase (conjugated estrogens/medroxyprogesterone acetate tablets)

General Correspondence

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

NDA SUPPLEMENT



Dear Dr. Allen:

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

In response to Ms. Diane Moore's request by telephone on October 17, 2000 for additional pharmacokinetic information as electronic files pertaining to NDA No. 04-782/S-115, enclosed with this submission are the following:

- Pharmacokinetics data for study 0713D2-119-US (hard copy previously submitted in support of these supplements) electronically in ASCII format with user guide (2 CDs are enclosed).
- Individual study report (GMR 32506) for 0713D2-119-US electronically in Word 97 on the same CDs as above.
- The Human Pharmacokinetics and Bioavailability Summary – Item 6.1 of NDA 04-782/S-115 – electronically in Word 97 (2 disks are enclosed).
- Dissolution data on the clinical lot and registration lots submitted in NDA 04-782/S-017 for Premarin Tablets 0.45 mg using USP 24 and the proposed modified USP 24 method with [ ] will be provided by January 12, 2001 as requested by Ms. Moore.

In addition to the above, pk data for study 0713D2-120-US (hard copy previously submitted in support of NDA No. 20-527/S-017) electronically in ASCII format with user guide and individual study report (GMR 32507) electronically in Word 97 are also provide on the same disks/CDs in response to a previous request.

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

Sincerely,

WYETH-AYERST LABORATORIES

Jennifer D. Norman

Jennifer D. Norman, Manager
Worldwide Regulatory Affairs

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

Meeting Minutes

Date: September 19, 2000 **Time**: 10:00 - 10:30 AM **Location:** Parklawn; Room 17 B43

NDA: 4-782/S-115 **Drug Name**: Premarin (conjugated estrogens, USP) tablets, 0.45 mg

Type of Meeting: Filing

Sponsor: Wyeth-Ayerst Research

Meeting Chair: Dr. Susan Allen

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Susan Allen, M.D., M.P.H. – Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Shahla Farr – Statistician, DBII (HFD-725)

Meeting Objective:
To discuss the fileability of Supplement 115 for the new 0.45 mg dose for the treatment of moderate to severe vasomotor symptoms associated with the menopause and the treatment of vulvar and vaginal atrophy.

Background: The primary goal date is May 31, 2001. The secondary goal date is July 31, 2001.

Decisions reached:
- Regulatory
  - fileable
  - an annotated label should be submitted; the submitted label does not appear to include changes from previous labeling
- Pharmacology
  - fileable; since CEE has been approved in higher doses, Pharmacology has no objections to filing
- Clinical
  - fileable
  - data for this supplement is a subset from the HOPE study; postmenopausal women with 7-8 moderate to severe hot flushes per day were included in the arms submitted for this supplement; 28

patients were in the 0.45 mg active drug arm and 30 patients were in the placebo arm of the study; these two arms are being compared in the efficacy analysis
    - maturation indexes at baseline and at 12 weeks were also included
- Statistics
    - fileable
    - data dictionaries are needed
    - SAS data sets were submitted electronically; a desk copy has been requested
- DSI
    - a DSI inspection is not warranted
- Financial Disclosure
    - pending
- Chemistry, Manufacturing and Quality Control
    - fileable
    - the sponsor is requesting a 2-year expiration date
    - there is no change in the drug substance or drug product; the new strength is colored blue with white ink in blister packs and 100 count bottles
    - the color of the clinical trial tablet and the to be marketed tablet are different; a dissolution test is needed to demonstrate that there is no difference between the two formulations (media to be used is to be determined)
    - the scale of the clinical lots is not the same as the scale for the marketed lots; this will be addressed during review
- Clinical Pharmacology and Biopharmaceutics
    - fileable
    - the dissolution methods used to evaluate the clinical lots were USP 22 and USP 23; the *in vitro* dissolution specifications methodology in USP 24 is different from the methodology in USP 23; this issue will be addressed during the review; the sponsor should submit dissolution data using USP 24
    - the Clinical Pharmacology, Biopharmaceutics reviewer requests that the sponsor provide pharmacokinetic data for study 0713D2-119-US/GMR-32506 in ASCII format with user guide as well as individual study reports and the Human Pharmacokinetics and Biopharmaceutics summary (Section 6) in WORD 97 software files

Action Items:

• **Item:**	**Responsible Person**:	**Due Date**:
• request PK data in ASCII format	Ms. Moore	1 week
• request annotated labeling	Ms. Moore	1 week
• request additional dissolution data using USP 24	Ms. Moore	during review

Signature, minutes preparer

Concurrence, Chair

Post Meeting Addendum: The sponsor should be requested to provide dissolution data using USP 24 methodology for the 0.45 mg strength tablet. The dissolution data should be submitted by January 12, 2001. The sponsor should also be requested to submit data using USP 24 with[ ]

drafted: dm/9.20.00/N4782/S-115FM91900

Concurrence:
TRumble 9.20.00/SAllen, LKammerman, DShames, Tvan der Vlugt 9.21.00/SSlaughter 9.27.00
JLau, SFarr, DLin 10.10.00/AParekh 10.16.00

NDA Arch:
HFD-580/Div File
HFD-580/SAllen/DShames/SSlaughter/Tvander Vlugt/TRumble/LKammerman/JLau/AParekh
HFD-580/DLin/MRhee

NDA 4-782/S-115

AUG 2 2000

PRIOR APPROVAL SUPPLEMENT

Wyeth-Ayerst Research
Attention: Joseph S. Sonk
Senior Director, Therapeutic Head, Women's HealthCare
Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Sonk:

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

Name of Drug Product:	Premarin (conjugated estrogens, USP) 0.45 mg tablet
NDA Number:	4-782
Supplement Number:	S-115
Therapeutic Classification:	Standard (S)
Date of Supplement:	July 31, 2000
Date of Receipt:	July 31, 2000

This supplement proposes the following change: A new low dose of Premarin (0.45 mg) for the treatment of moderate-to-severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 29, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be May 31, 2000, and the secondary user fee goal date will be July 31, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of

21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Diane Moore, BS, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Diane C. Rumble 8/2/00

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 4-782/S-115
HFD-580/Div. Files
HFD-580/D.Moore
HFD-580/SAllen/DShames/MMann/TvanderVlugt/DLin/MRhee/AParekh/JLau/LKammerman
HFD-580/AJordan/KRaheja
DISTRICT OFFICE

Drafted by: dm/August 2, 2000
Initialed by:
final:
filename: N4782AS115AK.doc

PRIOR APPROVAL SUPPLEMENT ACKNOWLEDGEMENT (AC)

WYETH-AYERST RESEARCH

BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

ORIGINAL

July 31, 2000

NDA No. 04-782
Premarin® (conjugated estrogens, USP) Tablets

Labeling Supplement:
Low Dose

Susan Allen, MD, Acting Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Attention: Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA NO. 4782 REF. NO. SE2-015
NDA SUPPL FOR new dosage

Dear Dr. Allen,

In accordance with 21 CFR §314.50 and §314.70(b), Wyeth-Ayerst Laboratories hereby submits a Supplemental New Drug Application for Premarin (conjugated estrogens, USP) tablets.

Marketing approval is being sought for a new low dose of Premarin (0.45 mg) for the treatment of moderate to severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy.

This supplemental NDA provides safety and effectiveness data regarding postmenopausal symptoms, endometrial and metabolic parameters for this new low dose of Premarin from the planned 1-year interim analysis of Protocol No. 713B-309-US[1] (the HOPE study). Data for the prevention of osteoporosis will be the subject of a separate Supplemental New Drug Application, submitted in a timely manner upon the completion of the HOPE study, currently anticipated to complete in 4Q 2000.

Please note that a separate SNDA based on interim data from the HOPE study was previously submitted to NDA No. 20-527 (S-017) on June 15, 2000 for new lower-doses of conjugated estrogens/ medroxyprogesterone acetate combination tablets; also for the treatment of moderate to severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy. The treatments being studied in the HOPE study include 4 strengths of conjugated estrogens/medroxyprogesterone acetate combination tablets, 3 strengths of Premarin tablets, and placebo. The pivotal clinical study report (GMR No. 38605) incorporated in NDA 20-527 S-017 is the same clinical study report that is submitted in this supplemental NDA (SNDA 04-782).

Clinical Study Background
Wyeth-Ayerst proposed to conduct a Phase IV clinical trial to define the minimum effective dose of the combination of conjugated estrogens and medroxyprogesterone acetate for the prevention of osteoporosis, during the October 5, 1993 meeting with the Division of Metabolism and Endocrine Drug Products (DMEDP) to discuss the filing of NDA No. 20-303 (Conjugated Estrogens and Medroxyprogesterone Acetate Separate Tablets). Several teleconferences and a face-to-face meeting were held with the Division to agree upon the final study design. The final protocol, 713B-309-US, was submitted on July 18, 1995.

[1] Subsequently designated as 713D2-309-US. The project code, 713B, was changed to 713D2 in order to comply with a new protocol numbering system.

This 8-arm, double blind (double-dummy), placebo and active-controlled, multicenter, out-patient trial is a 2-year study of lower-doses of the conjugated estrogens (CE) plus medroxyprogesterone acetate (MPA) combination and Premarin in postmenopausal women. The primary objective of the first year of treatment (basic study) was to evaluate the safety and efficacy of lower doses of CE/MPA in reducing the incidence of endometrial hyperplasia associated with the use of unopposed estrogen. The secondary objective was to evaluate the efficacy of lower doses of CE/MPA and Premarin in relieving menopausal vasomotor symptoms; the effects on vaginal maturation were also assessed.

The primary objective for the two-year treatment (Osteoporosis and Metabolic Substudy) is to satisfy the December 1994 Phase IV commitment to evaluate the safety and effectiveness of lower dose combinations of CE/MPA in the prevention of postmenopausal bone loss; metabolic data will also be analyzed. The establishing of the minimum effective dose for the prevention of osteoporosis will be the subject of a separate Supplemental to New Drug Application 20-527, submitted in a timely manner upon the completion of the HOPE study, currently anticipated to complete in 4Q 2000.

The products being studied in the 8 treatment arms are as follows:

CE oral tablets: 0.3 mg, 0.45 mg, and 0.625 mg
CE/MPA oral tablets: 0.3mg/1.5 mg, 0.45 mg/1.5, 0.45mg/2.5 mg, and 0.625 mg/2.5 mg
Placebo

Please recall that in a December 9, 1999 submission (IND No. 21,696, Serial No. 203), Wyeth-Ayerst provided a document entitled "Unblinding Procedures for Interim Analysis of the HOPE Study (713B-309-US)" which defined the unblinding strategy for the 1-year interim analysis. On December 16, 1999, Mrs. Diane Moore (Project Manager, DRUDP) telephoned JoAnne M. Bissinger (Wyeth-Ayerst) and indicated that the medical and statistical reviewers agreed that the unblinding procedures were appropriate. These procedures were implemented during the unblinding for the interim analysis.

User Fee
User Fee ID No. 3977 has been preassigned to this application. A check for 100% of the required fee ($142,870.00) for supplements requiring clinical data has been submitted to the Mellon Bank, Pittsburgh, PA postal address designated for user fee payments.

Field Copy
As requested by Ms. Debra Pagano (Program Coordinator for Field Copy Submissions) of the Philadelphia District Office (home office of Wyeth-Ayerst Laboratories) and in compliance with 21 CFR §314.50(l)(3), field copies were sent to the Buffalo, New York and San Juan, Puerto Rico District Offices on July 31, 2000.

Supplement Contents
In addition to the applicable Technical Sections, this supplement contains an abbreviated Application Summary consisting of draft Premarin annotated labeling, Chemistry, Manufacturing and Controls Summary, Human Pharmacokinetics and Bioavailability Summary, Clinical Data Summary and Results of Statistical analysis, and a Discussion of Benefit/Risk Relationship.

Item 11 Case Reports Tabulations

A teleconference was held with the Division on April 20, 2000 to discuss the electronic submission of Item 11 (Case Reports Tabulations). As agreed, one SAS XPORT file per data domain will include all patients in the study. Indicator variables on the files will identify patients included in each of the 3 populations (main study, patient of a disqualified investigator, and other patients who did not take study medication). The files are divided by investigator and sequential patient numbers. All demographic variables are included in the demographic data set; only demographics for gender, age, and ethnic group are included in other files included in this submission. An analysis data set for relief of moderate to severe vasomotor symptoms is also included.

The supplement contents are as follows:

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18	User Fee Cover Sheet	1
19	Other: A) Financial Disclosure, B) Pediatric Rule (Waiver Request)	1

If you have questions regarding this submission, please contact our representative, Miss JoAnne M. Bissinger, at (610) 902-3731 or the undersigned at (610) 902-3740.

Sincerely,

WYETH-AYERST LABORATORIES

Joseph S. Sonk
Senior Director,
Therapeutic Head, Women's Healthcare
Worldwide Regulatory Affairs

Premarin 0.45mg Cover Letter.doc

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE