

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-527/s-017

MEDICAL REVIEW(S)

Prempro™ Team Leader 2nd Cycle Review

NDA: 20-527, S-017
Drug: Prempro™
Claim: Protection of the endometrium from the development of estrogen-induced endometrial hyperplasia or cancer

Proposed Indications:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause

Dosage/Form/Route: 0.45 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate via oral tablet

Applicant: Wyeth Pharmaceuticals
Original Submission Date: June 15, 2000
2nd Cycle Receipt Date: September 12, 2002
Primary Review Completed: March 12, 2003
Date of Memorandum: March 12, 2003

On April 13, 2001, Prempro™ 0.45 mg CE/1.5 mg MPA received an approvable action from the Agency for the treatment of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause and the safety claim of prevention of endometrial hyperplasia in women with a uterus. The Sponsor was advised that a number of deficiencies were noted during inspection of the Guayama, Puerto Rico manufacturing facility and that before the application could be approved a satisfactory inspection of this facility would be required. In addition the Sponsor had to submit copies of final printed labeling revised according to the labeling enclosed with the approvable letter.

In a letter dated September 11, 2002, the Sponsor provided a complete response to the approvable letter of April 13, 2001 for NDA 20-527, S-017, stating the following:

1. **“Manufacturing facility** - With regard to the Guayama, Puerto Rico manufacturing facility and reference to the deficiencies noted by the inspector, subsequent to receiving the April 13, 2001 approvable letter, the facility was inspected by the Agency in March 2002 and has been found to be in cGMP compliance.”
2. **Final Printed Labeling** – Reference is made to our submission of revised proposed labeling for Prempro™, CE 0.45 mg/MPA 1.5 mg, as an amendment to NDA 20-527, S-017, dated July 31, 2002 as part of the complete response to the approvable letter.”

On January 31, 2003, the Investigations and Preapproval Compliance Branch, 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 20-527/S-017 (0.45 mg CE/1.5 mg MPA).

From a Chemistry, Manufacturing and Control (CMC) standpoint, this supplement is acceptable and may be approved. The following CMC issues were agreed upon between the Sponsor and the Division:

1. an interim release and stability specification for CE dissolution at the 5 hour timepoint; this interim acceptance criterion is _____
2. the Sponsor has committed to the identification of additional improved in-process controls at the _____ of conjugated estrogens tablet manufacture; once these improvements have been identified, three revalidation batches will be manufactured and subjected to room temperature and accelerated stability studies; the Sponsor anticipates that the results from these studies will be reported in 4thQ03.
3. _____

4. the Sponsor has committed to a Dissolution Surveillance Program for the dissolution of conjugated estrogens in the 0.45 mg/1.5 mg Premarin®/MPA drug product; in this commitment, every packaged lot will be tested for CE dissolution at six-month intervals; this surveillance program will be performed through expiration of the product.

The proposed labeling submitted on July 31, 2002 was modified in accordance with the 2003 draft guidance entitled, "Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Prescribing Information for Health Care Providers and Patient Labeling" (see **Federal Register**/ Volume 68/ Monday, February 3, 2003/Notices), and the PREMPRO™/PREMPHASE® approved labeling dated January 3, 2003. The medical officer review of March 12, 2003 delineates the specific revisions. Final labeling is attached to the action letter.

I concur with the Chemistry and Clinical review teams that deficiencies presented in the April 13, 2001 approvable letter have now been satisfactorily addressed and NDA 20-527. S-017 can be approved.

Shelley R. Slaughter, M.D., Ph.D.
Medical Officer Team Leader

**APPEARS THIS WAY
ON ORIGINAL**

**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
3/12/03 03:34:09 PM
MEDICAL OFFICER

Daniel A. Shames
3/12/03 06:17:13 PM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

Division Director's Memorandum

NDA#: 20-527S-017

Drug: Prempro™

Generic Drug Name: Conjugated estrogens (CE) and Medroxyprogesterone Acetate (MPA)

Indications

- 1) Treatment of moderate-to-severe vasomotor symptoms associated with the menopause
- 2) ~~————~~ vulvar and vaginal atrophy associated with the menopause

Dose: 0.45 mg CE/1.5 mg MPA

Administration: Daily administration

Formulation: Oral tablet

Applicant: Wyeth-Ayerst Research

Date of submission: June 15, 2000

Date of memorandum: April 13, 2001

Background

Prempro™ is an oral tablet containing CE and MPA that was initially approved for U.S. marketing in December of 1994. Two dosage strengths of Prempro™ are currently approved, one containing 0.625 mg of CE and 2.5 mg of MPA (Prempro™ 2.5) and one containing 0.625 mg of CE and 5 mg of MPA (Prempro™ 5).

At the time of initial approval of Prempro™, the FDA requested that the sponsor conduct a phase 4 study to evaluate the lowest dose combination of CE and MPA for the prevention of osteoporosis. The sponsor subsequently initiated a 2-year study (study 0713D2-309-US) to assess the safety and efficacy of a lower dose of Prempro™ for this indication.

The current efficacy supplement contains 1-year interim clinical data in support of approval of a low dose formulation of Prempro™ containing 0.45 mg of CE and 1.5 mg of MPA for the above noted indications. No data was provided in the current submission related to the prevention of osteoporosis indication. As described in the primary and secondary clinical reviews, the safety and efficacy of this low dose formulation of Prempro™ for the treatment of moderate-to-severe vasomotor symptoms and the treatment of vulvar and vaginal atrophy associated with the menopause was demonstrated from the interim data provided. It should be noted that the sponsor originally had also proposed a ~~————~~ ^M for approval in this submission but

As described in the Medical Officer memorandum dated April 13, 2001, the sponsor elected to withdraw this latter dosage strength during the current review cycle and resubmit additional, longer term data in support of approval of that dosage strength when available from the ongoing 2-year study.

The clinical, pharmacology/toxicology and biometrics disciplines all recommended approval of the 0.45 mg CE/1.5 mg MPA dosage strength of Prempro™ for the proposed indications. However, as described below, other review disciplines noted deficiencies in the current submission that precluded approval of the product during the current review cycle. These included:

Clinical Pharmacology and Biopharmaceutics:

The sponsor conducted two relative bioavailability studies in support of approval of low dose of Prempro™. These two studies were identical in design and demonstrated that (1) MPA does not alter the pharmacokinetics of CE, (2) MPA and some of the primary components of CE showed dose-proportionality, (3) the proposed *in vitro* dissolution method for CE was acceptable, and (4) the proposed *in vitro* dissolution method for MPA was acceptable on an interim basis.

The recommended *in vitro* dissolution specifications for the CE component of the 0.45 mg CE/1.5 mg MPA Prempro™ tablets are: not more than _____ estrone sulfate released at 2 hours; _____ estrone sulfate released at 5 hours; and not less than _____ estrone sulfate released at 8 hours. The sponsor agreed to these specifications. The recommended *in vitro* dissolution specification for the MPA component of the 0.45 mg CE/1.5 mg MPA Prempro™ tablets is not less than _____ MPA released at 30 minutes. Further development of the release methodology for MPA using dissolution equipment was recommended to the sponsor during a teleconference on April 11, 2001. Also during this teleconference, the sponsor agreed to conduct a feasibility dissolution study and submit preliminary dissolution data within 4 months of product approval to determine final dissolution specifications for the MPA component of the low dose Prempro™ product. This proposal was acceptable to the Clinical Pharmacology and Biopharmaceutics review team, and a written phase 4 commitment in this regard was obtained from the sponsor on April 12, 2001. With this commitment, the application was acceptable to this review discipline.

OPDRA:

The sponsor submitted a proposed tradename of _____ for this product. OPDRA did not recommend approval of this proposed tradename, noting that the Agency will no longer recommend approval of different proprietary names for products that are essentially identical to previously approved products from the same applicant or manufacturer. OPDRA recommended the continued use of the previously approved proprietary name PREMPRO for the new strength with the addition of strength modifiers. The sponsor accepted this recommendation but requested further discussion of this issue at a later date.

Chemistry

As described in the primary and secondary chemistry reviews, the drug substances for the low dose Prempro™ product are identical to those in the approved dosage strength tablets, and the drug product manufacturing process is identical to the approved process. Two sites perform drug product co-manufacturing for Prempro™ tablets, one located in Guayama, Puerto Rico and one in Rouses Point, NY. An Establishment Evaluation Request (EER) inspection of the Guayama, Puerto Rico manufacturing site resulted in an "WITHHOLD" recommendation for this site. This manufacturing site currently performs the functions of _____ and packaging of tablets into bottles and dial dispensers. This site also functions as an alternate site for branding and blister packaging of the dosage form.

As a result of these findings, the Chemistry review team concluded that the application should receive an approvable recommendation during the current review cycle.

Product Labeling:

The product labeling was significantly modified from that submitted with the application to bring the proposed label into compliance with modifications now required for all newly approved hormone replacement therapy products and to incorporate results from the data analyses performed during this review cycle. Final labeling negotiations will be concluded during a future review cycle if an "approval" recommendation is anticipated.

Conclusions and Recommendations:

I agree with the conclusions of all review disciplines and recommend that this application for the 0.45 mgCE/1.5 mg MPA dosage strength of Prempro™ receive an approvable action during the current review cycle. An approval recommendation for this application could be considered pending the following:

- 1) A satisfactory cGMP inspection of the Guayama, Puerto Rico drug product manufacturing facility;
- 2) An acceptable and agreed upon label for this product.

The sponsor has committed to conduct an MPA feasibility dissolution study and submit preliminary dissolution data from that study within 4 months of product approval to determine final dissolution specifications for the MPA component of the low dose Prempro™ product. Documentation of this commitment from the sponsor will be included in the approvable letter sent to the sponsor on April 13, 2001.

Susan S. Allen, MD, MPH
Director, HFD-580

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Susan Allen
4/13/01 04:30:06 PM
MEDICAL OFFICER

**APPEARS THIS WAY
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Prempro™ Team Leader Review

NDA: 20-527, S-017
Drug: Prempro™
Claim: Protection of the endometrium from the development of estrogen-induced endometrial hyperplasia or cancer

Proposed Indications:

1. Treatment of moderate-to-severe vasomotor symptoms
2. Vulvar and vaginal atrophy

Dosage/Form/Route: 0.45 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate via oral tablet

Applicant: Wyeth-Ayerst Research
Original Submission Date: June 15, 2000
Primary Review Completed: April 5, 2001
Date of Memorandum: April 5, 2001

Background and Regulatory History

Wyeth-Ayerst received approval for NDA 20-303 on December 30, 1994 to market Prempro™ and Premphase®, two oral combination drug products consisting of conjugated estrogens (CE) and medroxyprogesterone acetate (MPA). One dosage strength was approved, Prempro™2.5 (0.625 mg CE/2.5 mg MPA). Initially, Prempro™2.5 and Premphase® were co-packaged products. Prempro™ consisted of one tablet of CE and one tablet of MPA taken on a continuous daily basis and Premphase™ consisted of one tablet of CE taken on days 1-14 of the month and one tablet of CE and one tablet of MPA taken on days 15-28 of the month. On November 17, 1995, the Agency approved NDA 20-527 for Prempro™ 2.5, a single tablet of 0.625 mg CE/2.5 mg MPA taken on a continuous daily basis and Premphase™, a single tablet of CE taken for days 1-14 of the month and single tablet of 0.625 mg CE/2.5 mg MPA taken for days 15-28 of the month. NDA 20-527, supplement 006 for Prempro™ 5 (0.625 mg CE/5 mg MPA in a single tablet taken on a continuous daily basis) was approved on January 9, 1998. Prempro™ 2.5, Prempro™ 5, and Premphase™ are all approved for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause (VMS) in women with a uterus, 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. On June 5, 2000, Wyeth-Ayerst submitted NDA 20-527, supplement 017 (S-017) that presents the year 1 interim analyses of efficacy and safety data from Study 0713D2-309-US on the 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/ 1.5 mg MPA dosage strengths for VMS, VVA, and protection of the endometrium. Study 0713D2-309-US was a controlled clinical trial conducted to satisfy the post-approval Phase 4 commitment. No data is presented regarding the prevention of osteoporosis. The unblinding strategy to assemble and analyze the interim data for S-017 while preserving the integrity of the ongoing study was presented to the

Agency on December 9, 1999. The Agency concurred with the proposed unblinding procedures on December 16, 1999. Year 2 of Study 0713D2-309-US was ongoing at the time of submission of S-017. S-017 was filed on August 14, 2000. On April 3, 2001, the Sponsor proposed a dosage strength for consideration of approval during this review cycle. This review will summarize and address the Preclinical Pharmacology, Clinical Pharmacology and Biopharmaceutics, and Clinical reviews for this NDA supplement. Chemistry and Tradename issues will be discussed in the Deputy Division Director's review.

Preclinical Pharmacology and Toxicology

The Preclinical Pharmacology review notes that since the doses of conjugated estrogens and medroxyprogesterone acetate proposed in this supplement are lower than those already approved for this combination and the labeling is similar to the approved labeling, the Pharmacology Team has no concerns related to the Pharmacology and Toxicology of the 0.45 mg CE/1.5 mg MPA dosage strength. The Pharmacology team recommends approval of S-017.

Clinical Pharmacology and Biopharmaceutics

Two bioavailability studies are provided to support the clinical pharmacology and biopharmaceutics of S-017. These studies were both randomized, single dose, 4 period/treatment crossover studies. In Study 0713D2-119-US, the following estrogen/progestin combination or estrogen-alone doses were evaluated: 2 x 0.625 mg CE/2.5 mg MPA, 2 x 0.45 mg CE/ 2.5 mg MPA, 2 x 0.45 mg CE/1.5 mg MPA, and 2 x 0.45 mg CE. Study 0713 D2-120 evaluated 2 x 0.625 mg CE/2.5 mg MPA, 2 x 0.45 mg CE/1.5 mg MPA, 2 x 0.3 mg CE/1.5 mg MPA and 2 x 0.3 mg CE alone. The results of the two bioavailability studies demonstrate that CE and MPA behaved pharmacokinetically in a dose-related manner, and MPA had no effect on the pharmacokinetics of CE. The biopharmaceutics reviewer stated that the formulations (CE/MPA and CE), tested in the above bioavailability studies, are identical to the to-be-marketed formulations in terms of scale of manufacture and composition except in the color coat, which was white in the clinical formulation. The color change between the clinical batch and the to-be-marketed batch was justified by *in vitro* dissolution data.

The Sponsor's proposed *in vitro* dissolution method is acceptable. However, the recommended *in vitro* dissolution specifications are: at 2 hours 70% estrone sulfate released, at 5 hours 80% estrone sulfate released, at 8 hours not less than 90% estrone sulfate released. The Sponsor's proposed MPA *in vitro* dissolution method via a USP disintegration apparatus is acceptable on an interim basis. The recommended MPA specification for the 0.45 mg CE/1.5 mg MPA oral tablet is that not less than 80% MPA is released at 30 minutes. The Sponsor is encouraged to develop MPA dissolution methods via the USP *in vitro* dissolution apparatuses (basket and paddle) for the 0.45 mg CE/1.5 mg MPA tablet as well as all other approved dosage strengths of CE/MPA tablets. The final dissolution specification for the MPA component of the 0.45 mg CE/1.5 mg MPA tablet will be based on data via the USP *in vitro* dissolution apparatus.

As of the date of this memo, the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB DPEII) was awaiting a response from the Sponsor on the recommendations for the *in vitro* dissolution specifications before making a final recommendation and finalizing the review.

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

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

As indicated above, the Agency agreed with the plan to perform interim analyses of the data for VMS, VVA and protection of the endometrium. Only 9% (241) of the 2,673 treated subjects met the 1995 Guidance for Clinical Evaluation Of Combination Estrogen/Progestin-Containing Drug Products Used For Hormone Replacement Therapy of Postmenopausal Women (HRT Guidance)-specified number of moderate-to-severe vasomotor symptoms (7-8 per day or 50-60 per week) to be enrolled in a study to assess VMS. The Sponsor's original efficacy analysis for VMS utilized a baseline adjusted mean value and did not include last observation carried forward (LOCF). For consistency (with regard to the Label), the Sponsor was asked to provide efficacy analysis with the mean change and not baseline adjusted mean and to impute missing data with a LOCF approach. The efficacy analyses for those subjects meeting the requisite number of moderate-to-severe vasomotor symptoms (MSVS) are presented in Tables 1 and 2 which are modified from the medical officer's (MO) Table 4 and 5.

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/1.5 mg MPA n=29	Placebo n=28
Baseline Mean Number	12.61	11.69
Week 4 Mean Number Mean Change ^b p-value vs. placebo ^c	3.54 -8.98 <0.001	8.09 -3.80 N/A
Week 8 Mean Number Mean Change ^b p-value vs. placebo ^c	2.17 -10.39 <0.001	6.93 -4.86 N/A
Week 12 Mean Number Mean Change ^b p-value vs. placebo ^c	1.64 -10.92 <0.001	5.81 -5.98 N/A

^aLOCF = last observation carried forward

^bMean change from baseline

^cp-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/1.5 mg MPA n=29	Placebo n=28
Baseline Mean Severity	2.17	2.37
Week 4 Mean Severity Mean Change ^b p-value vs. placebo ^c	1.27 -0.99 <0.001	2.03 -0.29 N/A
Week 8 Mean Severity Mean Change ^b p-value vs. placebo ^c	0.84 -1.40 <0.001	1.76 -0.57 N/A
Week 12 Mean Severity Mean Change ^b p-value vs. placebo ^c	0.67 -1.54 <0.001	1.62 -0.72 N/A

^aLOCF = last observation carried forward

^bMean change from baseline

^cp-value is based on analysis of covariance with treatment as factor and baseline as covariate

The 0.45 mg CE/1.5 mg MPA dosage strength shows a statistically significant reduction in MSVS (frequency and severity) when compared to placebo at Week 4 and Week 12. There is a decrease of greater than 2 moderate-to-severe hot flushes per day in the 0.45 mg CE/1.5 mg MPA group compared to the placebo that is evident at Week 4 and maintained through Week 12. In addition, the Sponsor also performed subgroup analysis of VMS by age in those subjects who completed 12 weeks of treatment. The results by age group (<50, 50-59, and ≥ 60) showed that the 0.45 CE/1.5 mg MPA demonstrated a statistically significant treatment effect for both age groups (<50 and 50-59) at Weeks 4, 8, and 12. The ≥ 60 age group had too few women to permit an assessment of treatment effect.

The efficacy in treatment of VVA was assessed utilizing baseline, on-treatment and end-of-study vaginal cytology smears to determine the maturation Index (MI= the percentage of parabasal, intermediate and superficial cells). The Division now strongly recommends that studies for efficacy in the treatment of VVA assess physician-determined signs and patient's symptoms in addition to the MI. However, this recommendation was not being made when the original protocol for the HOPE study was reviewed. MI data is presented in Table 3 that was modified from the MO's Table 6.

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

Treatment	Baseline Mean \pm SE	Cycle 7 Mean Change \pm SE	Cycle 13 Mean Change \pm SE
0.45 mg CE/1.5 mg MPA			
Parabasal Cells (%)	6.6 \pm 0.7	12.2 \pm 1.0	13.5 \pm 1
Intermediate Cells (%)	54.3 \pm 2.1	18.2 \pm 2.0	19.4 \pm 2.1
Superficial Cells (%)	39.1 \pm 2.3	-30.4 \pm 2.2	-33.0 \pm 2.2
p-value vs. placebo		\leq 0.001	\leq 0.001
Placebo			
Parabasal Cells (%)	6.8 \pm 0.6	0.8 \pm 1.0	0.7 \pm 1.0
Intermediate Cells (%)	56.8 \pm 2.1	-3.2 \pm 2.0	-3.1 \pm 2.1
Superficial Cells (%)	36.5 \pm 2.3	2.4 \pm 2.2	2.3 \pm 2.2

Table 3 demonstrates that an estrogenic effect is shown at both cycle 6 and cycle 13 for the 0.45 mg CE/1.5 mg MPA dosage strength.

The efficacy in protection of the endometrium was evaluated based on the rate of endometrial hyperplasia and endometrial cancer as assessed by endometrial biopsy at baseline, between cycles 5-7 and between cycles 12-14. Endometrial hyperplasia is evaluated in clinical trials as a surrogate for endometrial carcinoma, because it is rare to see more than 1 to 2 endometrial cancers in most large clinical trials. Evaluable subjects were those who had taken at least one dose of study medication and had both a prestudy endometrial biopsy and an in-study endometrial biopsy performed during cycles 5 to 7 and cycles 12 to 14 or who developed endometrial hyperplasia at any time during the first year of the study. The study protocol followed the proposed revisions of the 1995 HRT Guidance document with respect to diagnosis of hyperplasia.

Two thousand one hundred fifty three (2,153) subjects were included in the primary analysis of endometrial hyperplasia and cancer by cycle 13. The Sponsor's analysis showed no endometrial cancer occurring during the course of the study. However, the clinical review led to a reclassification of two cases of hyperplasia (per the Sponsor) to endometrial carcinoma (per the clinical reviewers). The cycle 5-7 endometrial biopsy of subject 30924-0011 (0.3 mg CE) was read as complex hyperplasia with atypia by study pathologist 1 and endometrial adenocarcinoma, focal by study pathologist 2. The third adjudicating study pathologist, as specified in the protocol, did not read the slides. The patient withdrew from the study and had her slides re-read by an unblinded gynecologic oncologist, who agreed with the diagnosis of study pathologist 2. The Sponsor assigned this case as hyperplasia. However, because the third assessor was outside of the study and was not blinded, this diagnosis should not be considered. Taking into consideration the most conservative diagnosis ("worst case") between pathologist 1 and pathologist 2, the clinical reviewing team reclassified this diagnosis as endometrial adenocarcinoma.

The cycle 5-7 endometrial biopsy of subject 30912-0049 (0.45 mg CE/ 1.5 mg MPA) was read as complex hyperplasia with atypia in a polyp by pathologist 1, endometrial adenocarcinoma involving an endometrial polyp by pathologist 2, and endometrial adenocarcinoma in a polyp by pathologist 3. The Sponsor assigned this case as hyperplasia. The clinical review team reclassified this case as endometrial adenocarcinoma following the HRT Guidance document recommendation that the majority diagnosis, two of the three pathologists, is the accepted final diagnosis.

A third case was also reviewed for difficulty in the diagnosis. The cycle 5-7 endometrial biopsy of subject 30908-0003 (0.3 mg CE/1.5 mg MPA) was read as back-to-back glandular architecture, can not rule out hyperplasia by pathologist 1, complex hyperplasia with atypia by pathologist 2 and atypical glandular proliferation by pathologist 3. All three pathologists disagreed as to diagnostic severity. The Sponsor assigned this subject as hyperplasia. Following the HRT Guidance document scheme, since all three pathologists essentially disagreed, the clinical review team considered the worst case scenario and assigned this subject a diagnosis of complex hyperplasia with atypia.

The occurrence of 1 case of endometrial adenocarcinoma in the 0.45mg CE/1.5 mg MPA dosage strength produces an estimated endometrial carcinoma incidence rate of 0.37 (one-sided 95% CI [0, 1.]) for this group. 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 Hyperplasias	Hyperplasia rate (one-sided 95% CI)	p-value vs. CE alone
0.625 mg CE	249	20	8.03 (0, 11.5)	N/A.
0.625 mg CE/2.5 mg MPA	278	0	0.00 (0, 1.1)	<0.001
0.45 mg CE	279	9	3.23 (0, 5.6)	N/A
0.45 mg CE/2.5 mg MPA	273	0	0.00 (0, 1.1)	0.004
0.45 mg CE/1.5 mg MPA	272	0	0.00 (0, 1.2)	0.004
0.3 mg CE	269	0	0.00 (0, 1.1)	N/A
0.3 mg CE/ 1.5 mg MPA	272	1	0.37 (0, 1.8)	1.00
Placebo	261	0	0.00 (0,1.2)	

Typically 0 to 1 cases of endometrial carcinoma are seen in combination estrogen/progestin products in controlled clinical trials. This trial was not unusual in that one case of endometrial adenocarcinoma was seen in the 0.45 mg CE/1.5 mg MPA combination dosage strength. The rate of hyperplasia for this dosage strength (as well as all other CE/MPA combinations studied) clearly is acceptable when judged according to the recommendations made in the proposed revised 1995 HRT Guidance that the upper limit of a one-sided 95 % confidence interval for the risk of endometrial hyperplasia should not exceed 4%.

The rate of cumulative amenorrhea (percentage of subjects per treatment group who become amenorrheic and remain so throughout the study year) is presented in the label of combination estrogen/progestin products. The cumulative rate of amenorrhea was acceptable for the 0.45 mg CE/ 1.5 mg MPA dosage strength and was comparable at cycle 13 to that of 0.45 mg CE alone.

Two deaths were reported during Study 0713D2-309-US. Both of these were lung cancer deaths and were considered unrelated to study drug medication. Eight breast cancers were reported in the interim analysis at 1 year of study 0713D2-309. Seven of these cancers occurred during treatment and 1 case was diagnosed 1 year after treatment and is reported in the interim analysis. Four of the breast cancers were in the 0.3mg 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/1.5 mg MPA, the 0.45 mg CE/1.5 mg MPA and placebo treatment groups. No cases of breast cancer were seen in the 0.45 mg CE, the 0.45mg CE/2.5 mg MPA or the 0.3 mg CE treatment groups. Eight cases of breast cancer in 2,673 treated subjects do not represent a higher incidence of breast cancer in this trial than the incidence reported with other large HRT studies. Two additional cases of breast cancer have been reported in the 4-month update of safety, but they remain blinded as to treatment group. Other serious adverse events reported in the study include 4 cases of arterial

thrombosis, and three venous thromboembolic events. These numbers of these two events in a total of 2,673 subjects did not raise safety concerns for the clinical reviewers. A total of 266 subjects (10%) discontinued the study due to adverse events. Among the subjects treated in the combination estrogen/progestin groups the rate of discontinuation was 9%. The rate of discontinuations due to adverse events is not unusual for this size study and does not raise concern for safety. Women treated with CE alone (0.625 mg, 0.45 mg and 0.3 mg) in general had a more favorable increase in HDL-C and HDL₂-C concentrations than women treated with CE/MPA (0.625 mg CE/2.5 mg MPA, 0.45 mg CE/2.5 mg MPA, 0.45 mg CE/1.5 MPA and 0.3 mg CE/1.5 mg MPA). This is expected. However, the 0.45 mg CE/1.5 mg MPA demonstrates an acceptable lipid profile.

Conclusions and Recommendations

The safety and efficacy data presented in S-017 support the approval of the 0.45 mg CE/1.5 mg MPA dosage strength for the treatment of VMS and VVA in women with a uterus. The claim of protection of the endometrium is adequately supported. I concur with the recommendation of the primary clinical reviewer that the 0.45mg/1.5 mg MPA dosage strength can be approved.

Shelley R. Slaughter, MD, Ph.D.

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/s/

Shelley Slaughter
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MEDICAL OFFICER

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Medical Officer's Review

NDA 20-527/S-017
Supplemental Labeling Review

Date Submitted: 9/11/02
Date Received: 9/12/02
Review Finalized: 3/12/03

Sponsor: Wyeth Pharmaceuticals
P.O. Box 8299
Philadelphia, PA 19101-8299

Drug Name:
Generic: Conjugated Estrogens (CE)
Medroxyprogesterone Acetate (MPA)
Trade: Prempro™

Pharmacologic category: Estrogen

Dosage Form: Oral tablet

Strength: 0.45 mg CE/1.5 mg MPA

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 4-782

Background

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

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

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

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

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

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

Two dosage strengths of combined conjugated estrogens/medroxyprogesterone acetate (0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA) were submitted to the Agency on June 15, 2000 in NDA 20-527/S-017 for the treatment of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. On April 3, 2001, during the review cycle of NDA 20-527/S-017,

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

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

In a letter dated September 11, 2002, the Sponsor provided a complete response to the approvable letter of April 13, 2001 for NDA 20-527/S-017, stating the following:

1. **“Manufacturing facility** - With regard to the Guayama, Puerto Rico manufacturing facility and reference to the deficiencies noted by the inspector, subsequent to receiving the April 13, 2001 approvable letter, the facility was inspected by the Agency in March 2002 and has been found to be in cGMP compliance.”
2. **“Final Printed Labeling** – Reference is made to our submission of revised proposed labeling for Prempro, CE 0.45 mg/MPA 1.5 mg, as an amendment to NDA 20-527/S-017, dated July 31, 2002 as part of the complete response to the approvable letter.”

On January 31, 2003, the Investigations and Preapproval Compliance Branch, 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 20-527/S-017 (0.45 mg CE/1.5 mg MPA) and NDA 21-396 (0.3 mg CE/1.5 mg MPA and 0.45 mg CE/1.5 mg MPA).

Chemistry, Manufacturing and Controls

Please see the Chemistry, Manufacturing and Controls Review.

Final Labeling

Please see the attached PREMPRO™/PREMPHASE® label.

The proposed labeling submitted on July 31, 2002 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 PREMPRO™/PREMPHASE® approved labeling dated January 3, 2003.

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

Minor revisions have been made to the **Clinical Studies** subsections to update Table 3 under **Effects on vasomotor symptoms**, Table 5 under **Effects on the endometrium**, Figures 1 and 2 under **Effects on uterine bleeding or spotting**.

The _____ subsection has been deleted. A **Women's Health Initiative Studies** subsection (text and Table 10) has been added.

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

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

On February 6, 2003, the modified PREMPRO™/PREMPHASE® labeling was reviewed with the Sponsor during a teleconference. On March 6, 2003, the Sponsor resubmitted proposed draft PREMPRO™/PREMPHASE® labeling. Recommended changes to the proposed draft labeling submitted on March 6, 2003 include the following:

- 1) In Tables 1 and 2 the word “Arithmetic” has been added before Mean (%CV) under **PK Parameter** to read, “Arithmetic Mean (%CV)”.
- 2) In Table 5 the word _____ has been removed from the bullet under “No. (%) of patients with biopsies” so that the first line of the bullet reads, “hyperplasia/cancer”.
- 3) Footnote “a:” in Table 5 has been revised to read, “All cases of hyperplasia/cancer were endometrial hyperplasia except for 1 patient diagnosed with endometrial cancer based on endometrial biopsy.”
- 4) Footnote “b:” in Table 5 has been revised to read, “Two (2) pathologists evaluated each endometrial biopsy. Where there was lack of agreement on the presence or absence of hyperplasia/cancer between the 2, a third pathologist adjudicated (consensus).”
- 5) Under the **DOSAGE AND ADMINISTRATION** section the following paragraph has been added to # 1. For the treatment of moderate to severe vasomotor symptoms, and/or moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. “Patients should be started at PREMPRO 0.45/1.5 daily. In patients where bleeding or spotting remains a problem, after appropriate evaluation, consideration should be given to increasing the dose level. This dose should be periodically reassessed by the healthcare provider.”
- 6) In the **HOW SUPPLIED** section, National Drug Code (NDC) numbers have been added to each drug product.

Conclusions and Recommendations

From a clinical perspective, NDA 20-527/S-017 can be approved. The Sponsor should submit copies of final printed labeling revised as the enclosed labeling for NDA 20-527/S-017.

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

**Number of Pages
Redacted** 34



Draft Labeling
(not releasable)

**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
3/12/03 01:18:04 PM
MEDICAL OFFICER

Shelley Slaughter
3/12/03 01:34:07 PM
MEDICAL OFFICER
I concur.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-527/S-017

Date NDA Submitted: 6/15/00
Date NDA Received: 6/15/00
Review Completed: 3/22/01
Review Finalized: 4/6/01

**Medical Officer's Review
(Original Review)**

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

Drug Name:
Generic: Conjugated Estrogens (CE)
Medroxyprogesterone Acetate (MPA)

Pharmacologic category: Fixed combination estrogen and progestin

Route of Administration: Oral

Dosage Form: Tablet

Strength: 0.45 mg CE/1.5 mg MPA

Proposed Indications:
1) Treatment of moderate-to-severe vasomotor symptoms associated with the menopause.
2) vulvar and vaginal atrophy associated with the menopause.

Related Submission:

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ON ORIGINAL**

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EXECUTIVE SUMMARY

I. Recommendation

The reviewer recommends approval of TRADEMARK 0.45/1.5, henceforth in this review, referred to as 0.45 mg CE/1.5 mg MPA dosage strength or Prempro™ 0.45/1.5. 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 Prempro™ 0.45/1.5 for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause in women with a uterus, and protection of the endometrium.

II. Summary of Clinical Findings

Overview of the clinical program

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

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

Premphase® is also an approved product containing CE and MPA administered orally in a sequential regimen (CE alone administered orally on days 1-14 and CE/MPA administered orally on days 15-28 of a 28-day cycle) for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause. 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.

Prempro™ 0.45/1.5 (0.45 mg CE/1.5 mg MPA), the dosage strength that is the subject of NDA 20-527/S-017, was investigated in a single, controlled clinical trial to satisfy the post-approval Phase 4 commitment under NDA 20-303. Study 0713D2-309-US is an ongoing, prospective, double-blind, placebo/active drug-controlled clinical trial that randomized 2,805 postmenopausal women between 40 to 65 years of age to one of 8 treatment groups for a 2 year duration of treatment. Study 0713D2-309-US was designed to investigate the lowest dose combination of CE/MPA for the prevention of osteoporosis. In the sNDA submission, dated June 15, 2000, two dosage strengths were submitted for consideration of approval, 0.45 mg CE/1.5 mg MPA (TRADEMARK 0.45/1.5) and 0.3 mg CE/1.5 mg MPA (TRADEMARK 0.3/1.5).

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, and protection of the endometrium. 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 June 15, 2000.

Efficacy

Overall, the data presented shows that the 0.45mg CE/1.5 mg MPA dosage strength is effective in relieving moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy in generally healthy postmenopausal women between 40 and 65 years of age.

The data presented was obtained from an interim analysis of the 24-month, Phase 3 Health and Osteoporosis, Progestin and Estrogen (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.

The HOPE study investigated 8 treatment groups as summarized below:

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

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

For a VMS indication, the 1995 Hormone Replacement Therapy (HRT) Guidance 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/1.5 mg MPA dosage strength was effective in reducing both the number and severity of moderate-to-severe hot flushes at weeks 4 and 12, the primary efficacy time points for a VMS indication ($p < 0.001$ versus placebo at both time points).

Vaginal maturation index results (obtained from vaginal cytology smears collected at baseline, cycle 7 and cycle 13) in the HOPE study demonstrate a statistically significant estrogenic effect on vulvar and vaginal tissue for the 0.45 mg CE/1.5 mg MPA dosage strength. The maturation index represents the proportion of vaginal superficial cells relative to the number of parabasal and intermediate cells. The percentage of vaginal superficial cells increased significantly from baseline values at cycles 7 and 13 ($p < 0.001$ at both time points).

The efficacy of the 0.45 mg CE/1.5 mg MPA dosage strength for protection of the endometrium was also evaluated in Study 0713D2-309-US. Endometrial biopsies were obtained at baseline and twice during study year 1 (between cycles 5-7 and between cycles 12-14). A total of 2,153 evaluable subjects had a baseline endometrial biopsy, had taken at least one dose of study medication, and had an endometrial biopsy performed between cycles 5-7 and cycles 12-14 or were diagnosed with endometrial hyperplasia or cancer at any time during study year 1.

The Sponsor's analysis showed no endometrial cancer occurring during study year 1. However, two "endometrial malignancies" were recorded in the submission. Subject 30924-0011, in the 0.3 mg CE alone group, had an endometrial biopsy reading (scheduled biopsy at cycle 7) of endometrial adenocarcinoma by one primary pathologist during the trial, and a reading of complex hyperplasia with atypia by the other primary pathologist. The third, arbiter, pathologist was not consulted. Instead, the subject was referred to a private gynecologic oncologist who reviewed the study biopsy slides and recorded a diagnosis of severely atypical endometrial hyperplasia. Subject 30912-0049, in the 0.45 mg CE/1.5 mg MPA treatment group, also had a biopsy reading (scheduled biopsy at cycle 7) of endometrial malignancy during the trial. In this case, one primary pathologist and the arbiter pathologist agreed with a diagnosis of endometrial adenocarcinoma in a polyp. Following a repeat endometrial biopsy, primary pathologists 1 and 2 agreed with a diagnosis of complex hyperplasia with atypia in a polyp. In the submission, both of these subjects were classified as endometrial hyperplasia. A total of 32 cases of endometrial hyperplasia were reported across the 8 treatment groups.

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

Data on the remaining 30 cases of endometrial hyperplasia shows that the rate of endometrial hyperplasia with the 0.45 mg CE alone dosage strength was 3.23% (n = 279, one-sided 95% CI of 0, 5.6), while the rate of endometrial hyperplasia with the 0.45 mg CE/1.5 mg MPA dosage strength was 0.00% (n= 272, one-sided 95% CI of 0, 1.2). The 0.45 mg CE/1.5 mg MPA dosage strength demonstrated a lower rate of endometrial hyperplasia compared with 0.45 mg CE alone.

In the study results submitted, the rate of cumulative amenorrhea (percentage of subjects per treatment group who become amenorrheic and remain so throughout the study year) increased with each consecutive cycle. At cycle 13 the 0.45 mg CE/1.5 mg MPA dosage strength and the approved Prempro™ 2.5 (0.625 mg CE/2.5 mg MPA) produced similar cumulative amenorrhea rates of 62.8% and 62.2%, respectively.

Safety

CE and MPA have been used in combination HRT tablets since 1994. Their risks are well known. Overall, the treatment emergent adverse event profile of the 0.45 mg CE/1.5 mg MPA dosage strength is similar to that of the currently approved products, Prempro™ 2.5, Prempro™ 5, and Premphase®.

Safety evaluations and monitoring in the submitted study were adequate and complete for the 2,673 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.

Serious adverse events reported in the sNDA submission (across the 8 treatment groups) included 4 cases of arterial thrombosis, 3 venous thromboembolic events, five cases of cholelithiasis with cholecystectomy, and 8 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.

Seven of the 8 reported cases of breast cancer occurred during treatment. One case of breast cancer was diagnosed 12 months after completion of study medication and is included in the interim analysis. One CE alone treatment group (0.625 mg) reported one case of breast cancer. The placebo treatment group also reported one case of breast cancer. The remaining six cases of breast cancer 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 8 cases of breast cancer, reported in year 1 of the HOPE study, are not higher than reported in other large HRT clinical trials. Two

additional cases of breast cancer are reported in the 4-Month Safety Update. Both of these cases of breast cancer remain blinded because of the ongoing metabolic/osteoporosis substudy.

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

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

The 0.45 mg CE/1.5 mg MPA dosage strength was not studied in women with liver disease, and CE/MPA are contraindicated in postmenopausal women with liver dysfunction or disease. No studies were conducted in women with renal impairment in this submission. Prempro™ is contraindicated in pregnancy.

In a subgroup analysis by age across all 8 treatment groups (<50, 50 to 59, ≥ 60 years), the percentages of women with endometrial hyperplasia increased with age: 0.45% (2 cases in 446 subjects), 1.37% (20 cases in 1,454 subjects), and 3.56% (9 cases in 253 subjects), respectively. Twenty-nine of the 30 cases of endometrial hyperplasia 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.

**APPEARS THIS WAY
ON ORIGINAL**

CLINICAL REVIEW

I. Introduction and Background

Prempro™ 0.45/1.5 consist of two hormones, conjugated estrogens (CE) found in Premarin® tablets and medroxyprogesterone acetate (MPA), a derivative of progesterone. The proposed indications for Prempro™ 0.45/1.5 are: 1) the treatment of moderate-to-severe vasomotor symptoms associated with the menopause; and 2) vulvar and vaginal atrophy associated with the menopause. The Sponsor also proposed to demonstrate that this low dose CE/MPA combination

Prempro™ 0.45/1.5 is a lower dosage strength of the CE/MPA combination tablets (Prempro™ 2.5, Prempro™ 5, and Premphase®) that are currently approved for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause, and the prevention of osteoporosis in postmenopausal women with an intact uterus.

NDA 20-303, for Prempro™ and Premphase® was approved on December 30, 1994 with a commitment for a Phase 4 study to investigate the effectiveness of lower doses of Prempro™ on bone mineral density and endometrial endpoints. Initially, Prempro™ and Premphase® were co-packaged as one tablet of CE and one tablet of MPA. The Prempro™ regimen involved taking one tablet of 0.625 mg CE and one tablet of 2.5 mg MPA daily (two tablets total). The Premphase® regimen involved taking one tablet of 0.625 mg CE daily for 14 days followed by one tablet of 0.625 mg CE and one tablet of 5 mg MPA (two tablets total) daily for days 15-28 of a 28-day cycle.

NDA 20-527, also for Prempro™ 2.5 and Premphase®, was approved on November 17, 1995. NDA 20-527 provided for a single combined tablet of CE and MPA. Today, the Prempro™ regimen consists of the daily continuous oral administration of one single tablet of 0.625 mg CE plus 2.5 mg MPA. The Premphase® regimen consists of the daily continuous oral administration of one tablet of 0.625 mg CE on days 1-14 followed by the oral administration of one single tablet of 0.625 mg CE plus 5 mg MPA on days 15-28 of a 28-day cycle.

On January 9, 1998, NDA 20-527/S-006 was approved for Prempro™ 5. The Prempro™ 5 regimen consists of the daily continuous administration of a one single tablet of 0.625 mg CE plus 5 mg MPA. Prempro™ 5 is also approved for the treatment of moderate-to-severe vasomotor symptoms and vaginal atrophy associated with the menopause, and the prevention of osteoporosis in postmenopausal women with an intact uterus.

Overview of Clinical Section of sNDA

Study 0713D2-309-US, the Health and Osteoporosis, Progestin and Estrogen Study (HOPE) study, was undertaken to satisfy the agreed-upon post-approval Phase 4 commitment. The HOPE study is a 2-year clinical trial with the following 8 treatment groups:

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

Submitted with this application are the results of study year 1 of the HOPE study (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 or cancer, and maintaining an acceptable metabolic profile (metabolic substudy). Study year 2, ongoing in a subset of basic study subjects, is continuing 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,

No data from this study site is included in efficacy analyses.

Hormone Replacement Therapy Symptomatic Indications

The 1995 HRT Guidance entitled, "Guidance for Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products Used for Hormone Replacement Therapy in Postmenopausal Women" and the proposed revised 1995 HRT Guidance recommend 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 vaginal cytology smears are collected to determine the percentages of parabasal, intermediate and superficial cells (vaginal maturation index). In addition, the Division now strongly recommends that studies assess physician signs and subject self-assessment of symptoms at baseline and at end-of-study (initiated 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.

For a protection of the endometrium claim for a combination estrogen/progestin product, an endometrial biopsy specimen obtained prestudy and end-of-study (12 months or at study termination), and read by two primary independent, blinded pathologists using standardized criteria for the diagnosis of endometrial hyperplasia is needed. A third independent, blinded pathologist adjudicates diagnostic differences. The concurrence of two of the three pathologists is accepted as the final diagnosis (majority decision). If all three pathologists disagree on the final diagnosis, the most severe pathologic diagnosis is considered the final diagnosis.

Important Milestones in Product Development

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

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

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

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 HRT Guidance and the November 19, 1997 Committee for Proprietary Medicinal Products (CPMP), "Points to Consider on Hormone Replacement Therapy (CPMP/EWP/021/97) publication. The trial length, use of washout periods, inclusion criteria, measurements of hot flushes and endometrial hyperplasia endpoints were conducted as recommended in these documents.

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

Foreign Marketing Status

The currently approved Prempro™ 2.5, Prempro™ 5, and Premphase® are marketed in 32 countries worldwide.

Labeling Revisions and Status

Other Pharmacologically Related Agents

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

II. Clinically Relevant Findings from Chemistry, Toxicology, Microbiology, or Biopharmaceutics Reviews

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, 17 α -dihydroequilin, 17 β -dihydroequilin, 17 α -estradiol, 17 β -estradiol, equilenin, 17 α -dihydroequilenin, 17 β -dihydroequilenin, and $\Delta^{8,9}$ -dehydroestrone. Medroxyprogesterone acetate is a synthetic progestin derived from 17 α -hydroxyprogesterone.

The CE/MPA dosage form consists of a core tablet containing CE, which is coated with a

Please refer to the Chemistry, Manufacturing and Controls Review.

Pharmacology and Toxicology

Please refer to the Pharmacology Review.

III. Human Pharmacokinetics and Pharmacodynamics

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

In summary, the results of these two PK studies are as follows:

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

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

The CE/MPA formulation for 0.45 mg CE/1.5 mg MPA used in the clinical study was identical to the to-be-marketed formulation in terms of scale of manufacture and composition, but differed in color coat. The clinical formulation was white. The to-be-marketed color coat is gold (0.45 mg CE/1.5 mg MPA). However, the Clinical and Biopharmaceutics Review indicates that the dissolution profiles between the clinical batch and the market batch appear to be similar for the 0.45 mg CE/1.5 mg MPA tablet despite the color change.

No multiple dose (chronic administration) data is provided in the sNDA. The Clinical and Biopharmaceutics Review indicates that the lack of multiple dose PK information for 0.45 mg CE/1.5 mg MPA tablet may not be a critical issue for this efficacy supplement.

The Office of Clinical Pharmacology and Biopharmaceutics recommends that the Sponsor develop MPA *in vitro* dissolution methods via the USP *in vitro* dissolution apparatuses (basket and paddle) for the 0.45 mg CE/1.5 mg MPA tablet.

IV. Description of Clinical Data and Sources

Overall Data

In sNDA 20-527/S-017, the clinical development program consisted of two Phase 1 studies (Studies 0713D2-119-US and 0713D2-120-US and a large multicenter Phase 3 study (Study 0713D2-309-US) conducted in the US. The two Phase I studies were designed to describe the pharmacokinetics of the lower dose combination product (0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA). The Phase 3 study was designed to evaluate the impact of lower combination doses of CE/MPA on bone mineral density over a two-year period. This 2-year Phase 3 study is comprised of a basic study (year 1, total of 2,673 treated women of which 749 are substudy subjects), and a metabolic/osteoporosis substudy (years 1 and 2, approximately 749 women in substudy group).

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 is ongoing for the substudy population.

One additional study in Japan is also ongoing. Study is a 2-year prevention of osteoporosis study comparing two doses of CE/MPA and estriol. See Table 1 for a summary of studies in the clinical development program.

Table 1: Supplemental NDA 20-527 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 I study of the comparative bioavailability of conjugated estrogens and medroxyprogesterone acetate	CE/MPA Group A: 2 x 0.625 mg/2.5 mg Group B: 2 x 0.45 mg/2.5 mg Group C: 2 x 0.45 mg/1.5 mg CE alone Group D: 2 x 0.45 mg	31
0713D2-120-US	Completed, single-dose, 4-period, 4-treatment crossover design Phase I study of the comparative bioavailability of conjugated estrogens and medroxyprogesterone acetate	CE/MPA Group A: 2 x 0.625 mg/2.5 mg Group B: 2 x 0.45 mg/1.5 mg Group C: 2 x 0.3 mg/1.5 mg CE alone Group D: 2 x 0.3 mg	30
0713D2-309-US	Interim 1-year prospective, double-blind, randomized, Phase 3 study of multiple doses of conjugated estrogens and conjugated estrogens plus medroxyprogesterone acetate in postmenopausal women	Group A: 0.625 mg CE Group B: 0.625 mg CE/2.5 mg MPA Group C: 0.45 mg CE Group D: 0.45 mg CE/2.5 mg MPA Group E: 0.45 mg CE/1.5 mg MPA Group F: 0.3 mg CE Group G: 0.3 mgCE/1.5 mg MPA Group H: Placebo	348 331 338 340 331 326 327 332

Source: Adapted from sNDA 20-527, Volume 3, pages 70-74.

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 7 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)
- HDL₂-C
- Low-density lipoprotein cholesterol (LDL-C)
- lipoprotein (LP) (a)
- fibrinogen activity
- factor VIII activity
- antithrombin III activity
- plasminogen activator inhibitor-1 (PAI-1) antigen

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

In a December 9, 1999 submission to — 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 20-527, Addendum 2, Unblinding Procedures for Interim Analysis of HOPE Study, Volume 52, page 288). The Division concurred with the proposed unblinding procedures on December 16, 1999.

Study Demographics

The treatment groups were comparable in all demographics and baseline characteristics. See Table 2. Approximately 26-30% of treated subjects in each of the 8 treatment groups are 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 2: 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 20-527, Volume 53, Table 8.2A, pages 83-84.

^a mg dose of CE or CE/MPA.

SD = standard deviation.

Treatment Exposure

Of the 2,673 subjects treated, 2,341 received treatment with CE alone or CE/MPA, and 332 received placebo over a period of 12 months. One thousand twelve (1,012) subjects received at least one dose of CE alone and 1,329 subjects received at least one dose of CE/MPA. See Table 3.

Table 3: Assessments of Exposure^a to Active Medication

Parameter Days in Study	Group A 0.625 ^b	Group B 0.625/2.5 ^b	Group C 0.45 ^b	Group D 0.45/2.5 ^b	Group E 0.45/1.5 ^b	Group F 0.3 ^b	Group G 0.3/1.5 ^b
N	348	331	338	340	331	326	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 from sNDA 20-527, Volume 53, Table 10.1A, page 135.

^a Values represent the maximum possible exposure to study medication.

^b mg of CE or CE/MPA.

V. Clinical Review Methods

Materials Assessed in the Clinical Review of the sNDA

Data from two Pharmacokinetic Phase 1 Studies (Studies 0713D2-119-US and 0713D2-120-US), and a single Phase 3 clinical trial (Study 0713D2-309-US) were reviewed in detail. On October 16, 2000, the Sponsor submitted a 4-Month Safety Update. The 4-Month Safety Update summarized all relevant safety data for the HOPE study from December 23, 1999 (the cutoff date for the 1-year sNDA) to August 2, 2000.

Overview of Methods Used to Evaluate Data Quality and Integrity

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

Informed Consent and Standard of Patient Care

The informed consent document proposed for use in the clinical trial was 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.

Financial Disclosure Evaluation

VI. Review of Efficacy

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:

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

In addition to the above study medication, all study subjects received Caltrate®, elemental calcium, 600 mg, to be taken once daily. Therefore, each subject took three tablets daily, two tablets of study medication 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 participate 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 moderate-to-severe vasomotor symptoms 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:

$$\frac{[(\text{the number of mild hot flushes}) \times 1 + (\text{the number of moderate hot flushes}) \times 2 + (\text{the number of severe hot flushes}) \times 3]}{\text{the total number of hot flushes on that day}}$$

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 and 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 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 4, the 0.45 mg CE/1.5 mg MPA 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 4: Change in the Mean Number of Moderate-to-Severe Hot Flushes During Therapy in Subjects with ≥ 7 Moderate-to-Severe Hot Flushes at Baseline, ITT Population, LOCF

Week	Group E 0.45 mg CE/1.5 mg MPA ^a N = 29 of 331 (9%)	Group H Placebo N = 28 of 332 (8%)
Baseline		
Mean Number	12.61	11.69
Week 4		
Mean Number	3.54	8.09
Mean Change ^b	-8.98	-3.80
p-value vs. placebo ^c	<0.001	-
Week 8		
Mean Number	2.17	6.93
Mean Change ^b	-10.39	-4.86
p-value vs. placebo ^c	<0.001	-
Week 12		
Mean Number	1.64	5.81
Mean Change ^b	-10.92	-5.98
p-value vs. placebo ^c	<0.001	-

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

^a mg of conjugated estrogens/mg of medroxyprogesterone acetate.

^b Mean change from baseline.

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

Table 5 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/1.5 mg MPA 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 5: Change from Baseline in the Severity of Hot Flushes During Therapy in Subjects with ≥ 7 Moderate-to-Severe Hot Flushes at Baseline, ITT Population, LOCF

Week	Group E 0.45 mg CE/1.5 mg MPA ^a N = 29 of 331 (9%)	Group H Placebo N = 28 of 332 (8%)
Baseline		
Mean Severity	2.17	2.37
Week 4		
Mean Severity	1.27	2.03
Mean Change ^b	-0.99	-0.29
p-value vs. placebo ^c	<0.001	-
Week 8		
Mean Severity	0.84	1.76
Mean Change ^b	-1.40	-0.57
p-value vs. placebo ^c	<0.001	-
Week 12		
Mean Severity	0.67	1.62
Mean Change ^b	-1.54	-0.72
p-value vs. placebo ^c	<0.001	-

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

^a mg of conjugated estrogens/mg of medroxyprogesterone acetate.

^b Mean change from baseline.

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

One interesting observation across the 8 treatment groups, however, results from a subgroup analysis of VMS by age in subjects who completed 12 treatment weeks. Although the demographics and baseline characteristics for the VMS subset were not evaluated in the submission, supportive tables in the submission show that the majority of the VMS subset subjects were in the 50 to 59 age group with less in the < 50 age group and fewer in

the ≥ 60 age group. While the age subgroup numbers are too small to permit conclusions, they show interesting differences in treatment effect. Results by age group (< 50 , 50 to 59 , ≥ 60) demonstrate selected reduced or delayed treatment effect (reduction in frequency and severity of hot flushes) in women < 50 years of age compared to women 50 to 59 years of age. In the 50 to 59 age subgroup, a statistically significant reduction in the frequency and severity of hot flushes ($p < 0.001$) was demonstrated at all time points (weeks 4, 8, and 12). In women < 50 years of age, a statistically significant treatment effect was also demonstrated by the 0.45 mg CE/ 1.5 mg MPA dosage strength at all time points. This was not the case, however, for the 0.3 mg CE/ 1.5 mg MPA dosage strength, which showed a delay in treatment effect until week 8 for frequency ($p = 0.86$ at week 4, $p = 0.024$ at week 8), and no treatment effect for severity at any time point ($p = 0.065$ at week 4, $p = 0.25$ at week 8, and $p = 0.28$ at week 12). The ≥ 60 age group had too few women to permit an observational assessment of treatment effect.

Vaginal Maturation Index

A vaginal cytological smear was obtained at the prestudy visit and during cycles 7 and 13 to determine the vaginal maturation index (VMI). A VMI is 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 7 and cycle 13 on March 22, 2001. See Table 6.

The VMI results show that the percentages of vaginal superficial cells increased significantly from screening values at cycles 7 and 13, and the differences were statistically significant from placebo for the 0.45 mg CE/ 1.5 mg MPA 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 6: Subjects with Maturation Index Results, Mean Value and Comparison Between Prempro™ 0.45/1.5 and Placebo by Cycle, Intent-to-Treat Population with LOCF

Treatment ^a (N) Type of Cell	Percentage of Epithelial Cells (%)			
	Baseline Mean \pm SE	Cycle 7 Mean Change \pm SE	Cycle 13 Mean Change \pm SE	p-Value vs. Placebo ^b Cycle 6 - Cycle 13
Group E (n = 319) 0.45 mg CE/1.5 mg MPA				
Superficial Cells	6.6 \pm 0.7	12.2 \pm 1.0	13.5 \pm 1.0	<0.001 - <0.001
Intermediate Cells	54.3 \pm 2.1	18.2 \pm 2.0	19.4 \pm 2.1	<0.001 - <0.001
Parabasal Cells	39.1 \pm 2.3	-30.4 \pm 2.2	-33.0 \pm 2.2	<0.001 - <0.001
Group H (n = 321) Placebo				
Superficial Cells	6.8 \pm 0.6	0.8 \pm 1.0	0.7 \pm 1.0	<0.001 - <0.001
Intermediate Cells	56.8 \pm 2.1	-3.2 \pm 2.0	-3.1 \pm 2.1	<0.001 - <0.001
Parabasal Cells	36.5 \pm 2.3	2.4 \pm 2.2	2.3 \pm 2.2	<0.001 - <0.001

Source: Adapted from data provided by the Sponsor on March 22, 2001.

^a Identified by dose (mg) of CE or CE/MPA.

^b Based on analysis of variance.

Protection of the Endometrium

For study year 1, the primary efficacy measure was an assessment of the incidence of endometrial hyperplasia made by endometrial biopsy. In year 1 of Study 0713D2-309-US, endometrial biopsies were obtained at cycles 7 and 13. The population of interest was an efficacy-evaluable population. Evaluable subjects are those who had a prestudy endometrial biopsy, had taken at least one dose of study medication, and had an endometrial biopsy performed during cycles 5 to 7 and cycles 12 to 14 or who developed endometrial hyperplasia at any time during the first year of the study.

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).

Fisher's exact test was used to compare the incidence of endometrial hyperplasia between groups. At each of the 3 dose levels of CE, the CE/MPA dose combination(s) were compared with CE alone at the comparable dose. The placebo group was not used in the comparisons to evaluate the incidence of endometrial hyperplasia because it provides no information on the influence of estrogen-induced hyperplasia or the protective effect of MPA.

A total of 2,153 subjects were included in the primary efficacy analysis of endometrial hyperplasia or cancer at cycle 13. Five hundred twenty (520) subjects were excluded because no valid endometrial biopsy was obtained between cycles 12 to 14 and no endometrial hyperplasia was diagnosed before cycle 12. One of these subjects did not have a prestudy endometrial biopsy performed.

The incidence of endometrial hyperplasia at cycle 13 was calculated as follows:

$$I = A/B$$

where I = incidence at Cycle 13 evaluation

A = number of subjects with biopsies positive for endometrial hyperplasia during the first 14 cycles

B = number of subjects with biopsies during cycles 12 through 14 meeting the criteria specified for the efficacy-evaluable population, plus number of subjects with biopsies positive for endometrial hyperplasia before cycle 12.

According to the Sponsor, no endometrial carcinoma developed during the clinical study. However, two subjects had endometrial biopsy readings of endometrial carcinoma in the 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 (age 58) 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 (endometrioid/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 4/20/99

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 (age 63) 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

_____, the clinical review team followed the most conservative approach and accepted the "worst-case" diagnosis of endometrial adenocarcinoma rendered by pathologist 2. If the most conservative approach is 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.

- Subject 30908-0003 (age 57) in Group G (0.3 mg CE/1.5 mg MPA)

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 7/24/96

Pathologist 1 =

Single fragment with metaplastic cells, back to back glandular architecture; cannot rule out hyperplasia; recommend full D&C for more definitive diagnosis.

Pathologist 2 =

Complex hyperplasia with atypia; cannot rule out peculiar degenerating metaplasia or carcinoma; recommend D&C if clinically indicated.

Pathologist 3 =

Atypical glandular proliferation; cannot tell if this is of endometrial or endocervical origin; it may represent an atypical microglandular hyperplasia of endocervix, but I am more worried about adenocarcinoma; further investigation is recommended.

Study medication stopped on 9/11/96
D&C performed on 9/13/96

Pathologist 1 =

Glandular proliferation with mucinous differentiation; microglandular hyperplasia of endocervix vs. endometrial hyperplasia; tissue insufficient for definitive diagnosis.

Pathologist 2 =

Atypical glandular tissue consistent with well-differentiated endocervical adenocarcinoma and minute fragments of benign endometrium; fractional D&C/ECC may be helpful at delineating exact origin of neoplasm.

Hysterectomy performed on 10/23/96

Surgical pathology report =

Atrophic endometrium with focus of glandular complexity consistent with hyperplasia; no cytologic atypia.

Reviewer's Comments

The three pathologists disagreed on the cycle 7 histological classification. Following the proposed revised 1995 HRT Guidance recommended procedure, of accepting the worst case scenario when there is disagreement between the three pathologists, the diagnosis of complex hyperplasia with atypia is accepted as the final diagnosis.

The two additional requested reports covered subjects (Subject # 30936-0006; Subject #30908-0002) in treatment Group A (0.625 mg CE). The reviewer concurs with the diagnosis of endometrial hyperplasia in both cases.

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.

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, 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 Group E and Group F). Therefore, a total of 30 subjects developed endometrial hyperplasia and 2 subjects developed endometrial adenocarcinoma.

Twenty-nine (29) of the cases of endometrial hyperplasia occurred in the CE alone treatment groups. Only 1 case of endometrial hyperplasia occurred in a CE/MPA group (0.3 mg CE/1.5 mg MPA). In Table 7, 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) compared to Group F (0.00%). See Table 7.

Table 7: 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 20-527, Volume 53, page 96.

^a Total number of hyperplasias calculated as number of patients.

^b Confidence intervals calculated by the statistical reviewer.

^c Individual pairwise comparisons: Groups B with A; D and E with C; G with F, based on Fisher' exact test. Two-sided p-values are shown.

However, endometrial hyperplasia or endometrial cancer were reported in treatment groups in Study 0713D2-309-US. Table 8 shows the incidence rates for hyperplasia or cancer when the cases of endometrial hyperplasia or cancer are combined.

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

Treatment by dose (mg) of CE or CE/MPA	N	Total Number Hyperplasia/ Carcinoma ^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	1	0.37	(0, 1.8)	0.020
Group F 0.3 mg CE	269	1	0.37	(0, 1.8)	--
Group G 0.3 mg CE/1.5 mg MPA	272	1	0.37	(0, 1.8)	1.00
Group H Placebo	261	0	0.00	(0, 1.2)	--

Source: Prepared by the Division from combined numbers of hyperplasia or cancer.

^a Total number of hyperplasias or cancer calculated as number of patients.

^b Confidence intervals calculated by the statistical reviewer.

^c Individual pairwise comparisons: Groups B with A; D and E with C; G with F, based on Fisher' exact test. Two-sided p-values are shown.

Reviewer's Comments

The reported 1-year incidence rates of endometrial hyperplasia are approximately 0-1% for non-treated women and women treated with currently marketed HRT regimens, including Prempro™ 2.5, Prempro™ 5, and Premphase®. Per the proposed revised 1995 HRT Guidance, for protection of the endometrium, the upper limit of a one-sided 95% confidence interval for the risk of endometrial hyperplasia should not exceed 4%.

Results from Study 0713D2-309-US show the occurrence of two endometrial cancers, one in the 0.3 mg CE alone group (Group F) and one in the 0.45 mg CE/1.5 mg MPA group (Group D). However, calculating the combined endometrial hyperplasia or cancer rate for the 0.45 mg CE/1.5 mg MPA dosage strength, an incidence rate of 0.37% for hyperplasia or cancer is found with a one-sided 95% confidence interval of 0, 1.8, well below the one-sided 95% confidence interval upper limit of 4%.

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

Reviewer's Comments

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

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

Reviewer's Comments

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

The data presented in Table 7 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 case of hyperplasia was 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.