CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-527/S-006

MEDICAL REVIEW(S)

Medical Officer's Original Review of Efficacy Supplement

NDA 20,527/S-006

Drug:	Prempro™	Submission Date:	1/8/97
Sponsor:	Wyeth-Ayerst Research	Date Received:	1/9/97
	P.O. Box 8299	Date assigned:	1/14/97
	Philadelphia, PA 19101-8299	Review Completed:	12/3/97
		Review Finalized:	12/22/97

1. General Information

Generic Name of Drug:	Conjugated Estrogens (estrone sulfate and equilin sulfate) and Medroxyprogesterone Acetate Tablets, USP
Trade Name of Drug:	Prempro™ (continuous combined regimen)
Pharmacologic Category:	Fixed combination oral estrogen and progestin
Indications:	In women with an intact uterus: 1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of vulvar and vaginal atrophy. 3. Prevention of osteoporosis
Dosage Form:	Combination Tablet containing Conjugated Estrogens, 0.625 mg/Medroxyprogesterone Acetate, USP, 5 mg
Route of Administration:	Oral
Proposed Clinical Use:	Provide for the continuous combined dosing regimen of 0.625 mg conjugated estrogens (CE)/5 mg medroxyprogesterone acetate (MPA) for Prempro Tablets
NDA Drug Classification:	3S
Related Submissions:	NDA 20,303, NDA 20, 527

Resume

Prempro™ containing conjugated estrogens (CE) and medroxyprogesterone acetate (MPA), is an approved drug. Originally under NDA 20,303, this product was marketed as separate tablets of Premarin (0.625 mg) and Cycrin (2.5 mg) blister packaged together for concomitant usage as a continuous regimen product for indicated usage in postmenopausal women with intact uteri for the treatment of moderate to severe vasomotor symptoms associated with the menopause, vulvar and vaginal atrophy, and the prevention of osteoporosis. This approval, granted in December 1994, was based on the results of a well-controlled clinical trial which demonstrated a reduction in the one-year incidence of endometrial hyperplasia with the approved combination regimen to 1% or less, compared with 8 - 20% hyperplasia rate observed with Premarin™ 0.625 mg/day. Approval was also granted in 1994 for Premphase™ (Premarin 0.625 mg for daily administration/Cycrin 5.0 mg for concomitant administration days 15-28 of each 28 day cycle).

Based on the safety and efficacy findings with separate Premarin and MPA tablets (under NDA 20,303), under NDA 20,527, a new single, combination tablet consisting of a Premarin tablet core with a thin sugar-coating containing medroxyprogesterone acetate applied was approved in November 1995 (for both Prempro [Premarin 0.625 mg/MPA 2.5 mg for continuous daily use] and Premphase [Premarin 0.625 mg/d x days 1-14 and Premarin 0.625 mg/MPA 5.0/d x days 15-28 of each 28 day cycle]). The submitted safety database under NDA 20,527 included information from [redacted] and spontaneous reports from the [redacted] database maintained by Wyeth-Ayerst for the period from 6/16/94 to 6/15/95 (see Medical Officers Review of NDA 20,527). Efficacy of the combination tablet regimen was determined by reference to the separate tablet regimen of Prempro, which was studied in the large-scale clinical trial reported in NDA 20,303. Evidence was provided that the Prempro combination tablet formulation was adequately manufactured and bioequivalent to its respective separate tablet formulation in single-dose pharmacokinetics studies administered both with and without food. Once NDA 20,527 was approved the marketing of separate tablets under NDA 20,303 was phased out.

All treatment regimens in the pivotal trial in NDA 20,303 included the lowest Premarin dose (0.625 mg) previously shown to preserve bone mineral density and prevent osteoporosis. The treatment doses were as follows:

- Regimen A (Premarin 0.625 mg/MPA 2.5 mg/day continuously),
- Regimen B (Premarin 0.625 mg/MPA 5.0 mg/day continuously),
- Regimen C (Premarin 0.625 mg daily/MPA 5.0 mg/day x days 15-28/per 28 day cycle),
- Regimen D (Premarin 0.625 mg daily/MPA 10.0 mg/day x days 15-28/per 28 day cycle), and
- Regimen E (Premarin 0.625 mg/Placebo/ day continuously).

Per the sponsor, there were no statistically significant differences in the incidence of endometrial hyperplasia between any Premarin/MPA treatment groups or between continuous combined regimens A and B and sequential groups regimens C and D at 6-months or at the 12-month evaluation. Per the Medical Officer's Review, "Given that the 1-year efficacy results with regimen B (Premarin 0.625 mg/MPA 5.0 mg/day continuously) and regimen A (Premarin 0.625 mg/MPA 2.5 mg/day continuously) were indistinguishable, and that regimen B contains twice as much MPA as regimen A, there is no efficacy justification to approve regimen B. Since no compelling safety benefit of regimen B over regimen A has been shown in the NDA, there is also no safety justification to approve regimen B. Although the incidence of irregular bleeding was lower with regimen B (13% of cycles) than with regimen A (22% of cycles), this statistically significant difference was not clinically significant because it was not associated with increased dropout or decreased compliance with study medication by subjects randomly assigned to regimen A, compared with regimen B or any other treatment regimen." Approval was granted for a single Prempro dosage form (Premarin 0.625 mg/MPA 2.5 mg for continuous daily use), and a single Premphase dosage form (Premarin 0.625 mg/day for days 1-14 and Premarin 0.625 mg/MPA 5.0 mg per day for days 15-28 of each 28 day cycle).

This submission (NDA 20-527/S-006) requests approval of the previously reviewed Prempro dosage form of Premarin 0.625 mg/MPA 5.0 mg/day continuously for each 28 day cycle and includes two attachments: Attachment I, "Recommendations Of Expert Consultants On The Premarin® 0.625 mg/MPA 28-Day Continuous Combined Regimen"; and Attachment II, "Continuous Combined Hormone Replacement Therapy Study: Market Research Study of Physician Use Of 5 mg Progestin In Combination With Estrogen."

Summary of Submission

Attachment I: "Recommendations Of Expert Consultants On The Premarin® 0.625 mg/MPA 28-Day Continuous Combined Regimen."

The sponsor's "panel of experts" were provided with review materials including the Medical Officer's Review (MOR) of NDA 20,303, two volumes of reports for pivotal studies 713B-300 and 713B-301 conducted by the sponsor in support of NDA 20,303, and supplemental bleeding presentations requested by the FDA. The "experts" considered the following issues raised by the MOR:

1) Was there a significant advantage in using a continuous combined regimen of 0.625 mg Premarin/5.0 mg MPA compared with a continuous combined regimen of 0.625 mg Premarin/2.5 mg MPA with respect to the bleeding profiles (primarily amenorrhea) in postmenopausal women?
2) If an advantage existed, was it clinically meaningful and what effect would it have with respect to compliance?
3) Can the fact that only a few subjects withdrew from hormone replacement therapy (HRT) treatment groups because of irregular bleeding in a 1-year clinical trial be used to determine that such bleeding is not a clinically significant issue in treating postmenopausal women in medical practice?
4) Was there a safety issue in using 5.0 mg MPA in the above continuous combined regimen compared with using 2.5 mg MPA?
5) In particular, was the risk of breast cancer exacerbated by a 5.0 mg dose of MPA as opposed to a 2.5 mg dose in a continuous combined regimen with a 0.625 mg dose of Premarin?
6) How important is it to a physician treating postmenopausal women with HRT to have the flexibility to titrate the doses of estrogen and progestin to suit individual subject needs?

In response to issues 1 and 2 above the "expert panel" re-reviewed the pivotal bleeding data under NDA 20,303. The manner in which data concerning bleeding associated with endometrial biopsies was presented was one issue the panel reviewed. In the initial protocol for study 713B-300 conducted by Wyeth-Ayerst, bleeding associated with an endometrial biopsy on the day of the biopsy and for 2 days thereafter was to be excluded from analysis (the endpoint definition of amenorrhea in Protocol 713B-300 = amenorrhea as absence of bleeding or spotting minus the number of bleeding days considered secondary to endometrial biopsy). However, after the blind was broken and the data analyzed, Wyeth-Ayerst (ostensibly recognizing that the approved two-day window was "unnecessarily rigorous") presented amenorrhea data with a 6-day window for bleeding associated with an endometrial biopsy in the NDA 20,303 submission. In summary, this 6-day window analysis presenting the overall (total cycles) incidence of "irregular bleeding" for the continuous regimens (regimen A = Premarin 0.625 mg/MPA 2.5 mg; regimen B = Premarin 0.625 mg/MPA 5 mg) showed that regimen A had the higher incidence of "irregular bleeding" (22.3% versus 12.7% of cycles) and "irregular spotting" (16.2% versus 14.4% of cycles) (see adapted Table 1 and Table 2; source is NDA 20,303, volume 1.40, pages 59-60). Additionally, the sponsor claimed that after the first 6 cycles (cycles 7 through 13, using a 6-day window), amenorrhea occurred in a significantly greater percentage of subjects treated with continuous regimen B (101 patents/47.4% of "enrolled"; 101 patients/52.6 % of "completed" subjects) than regimen A (82 patients/37.4% of "enrolled"; 82 patients/40.4% of "completed" subjects) (see adapted Table 3; source is NDA 20,303, volume 1.40. page 62). Following review, the medical reviewer considered such post-hoc re-definition of the bleeding endpoints to be inappropriate and recommended that the analysis not be accepted to support labeling claims.

In a labeling follow-up, submitted by the sponsor on January 12, 1995, amenorrhea data using the 2-day window was presented (see adapted Table 4). The incidence of amenorrhea for at least cycles 7 through 13 (2-day window for all treatment groups) was again higher with continuous regimen B (93 patients/43.7% of "enrolled"; 93 patients/48.4% of "completed" subjects) than regimen A (73 patients/33.3% of "enrolled"; 73 patients/36% of "completed" subjects). Although the percent of patients experiencing amenorrhea is lower with the 2-day window (a decrease of approximately 4% when the 2-day window is used instead of the 6-day window), the same statistically significant pairwise differences occur between Groups A, B, and E (Premarin alone).

In its review, the "expert panel" also completed a bleeding analysis for regimen B with a 2-day window for bleeding associated with endometrial biopsies (see NDA 20,527/S-006, pages 12-13). The comparative 2-day window results between regimens A and B were reviewed by the panel and they concluded that the incidence of consecutive cycles of amenorrhea was similar for subjects on regimen A and regimen B regardless of whether a 2-day or a 6-day window was used. The panel concluded that, regardless of how the data was analyzed, there was a statistically significant and clinically meaningful difference favoring regimen B over A in consecutive cycles of amenorrhea in later cycles (NDA 20,527/S-006, pages 3-4).

Table 1

Incidence (%) of Cycles with Irregular Bleeding During Treatment (6-day window)

	Continuous Regimens				Sequential Regimens				Premarin Alone	
	A: Prem/MPA (0.625 mg/2.5 mg)		B: Prem/MPA (0.625 mg/5.0 mg)		C: Prem/MPA (0.625 mg/5.0 mg)		D: Prem/MPA (0.625 mg/10.0 mg)		E: Prem/Placebo (0.625 mg)	
Cycle	No. of Cycles(%)	Cycles w/ Bleeding*	No. of Cycles(%)	Cycles w/ Bleeding	No. of Cycles(%)	Cycles w/ Bleeding	No. of Cycles(%)	Cycles w/ Bleeding	No. of Cycles(%)	Cycles w/ Bleeding
2	313	107 (34.2)[BCDE]	308	71 (23.1)[ACDE]	322	36 (11.2)[AE]	322	33 (10.2)[AE]	320	26 (8.1)[AE]
5	301	63 (20.9)[BCD]	292	32 (11.0)[A]	293	32 (10.9)[A]	294	23 (7.8)[AE]	300	47 (15.7)[B]
8	284	54 (19.0)[BCD]	284	23 (8.1)[AE]	284	20 (7.0)[AE]	277	18 (6.5)[AE]	265	37 (14.0)[BCD]
11	277	36 (13.0)[B]	276	16 (5.8)[AE]	277	22 (7.9)[E]	271	22 (8.1)[E]	255	45 (17.6)[BCD]
Total Cycles	3782	844 (22.3)	3726	475 (12.7)	3772	307 (8.1)	3732	311 (8.3)	3639	532 (14.6)

* Bleeding = irregular bleeding with or without spotting.
A,B,C,D,E = Significantly ($p < 0.05$) different from treatment group(s) a,b,c,d,e respectively.

All groups received 0.625 mg Premarin daily; Group A received 2.5 mg MPA daily, Group B received 5.0 mg MPA daily, Group C received 5.0 mg MPA daily for days 15-28, Group D received 10.0 mg MPA daily for days 15-28, Group E did not receive MPA.

SOURCE: NDA 20,303, volume 1.40, page 59

Table 2

Incidence (%) of Cycles with Irregular Spotting During Treatment (6-day window)

	Continuous Regimens				Sequential Regimens				Premarin Alone	
	A: Prem/MPA (0.625 mg/2.5 mg)		B: Prem/MPA (0.625 mg/5.0 mg)		C: Prem/MPA (0.625 mg/5.0 mg)		D: Prem/MPA (0.625 mg/10.0 mg)		E: Prem/Placebo (0.625 mg)	
Cycle	No. of Cycles	Cycles w/ Spotting*	No. of Cycles	Cycles w/ Spotting	No. of Cycles	Cycles w/ Spotting	No. of Cycles	Cycles w/ Spotting	No. of Cycles	Cycles w/ Spotting
2	313	43 (13.7)[BE]	308	63 (20.5)[ACDE]	322	29 (9.0)[B]	322	43 (13.4)[BE]	320	22 (6.9)[ABD]
5	301	49 (16.3)[CE]	292	49 (16.8)[CE]	293	26 (8.9)[AB]	294	35 (11.9)	300	31 (10.3)[AB]
8	284	56 (19.7)[BCE]	284	29 (10.2)[A]	284	30 (10.6)[A]	277	37 (13.4)	265	31 (11.7)[A]
11	277	33 (11.9)	276	21 (7.6)	277	24 (8.7)	271	23 (8.5)	255	30 (11.8)
Total Cycles	3782	614 (16.2)	3726	537 (14.4)	3772	328 (8.7)	3732	412 (11.0)	3639	358 (9.8)

* Spotting = spotting alone.
A,B,C,D,E = Significantly ($p < 0.05$) different from treatment group(s) a,b,c,d,e respectively.

All groups received 0.625 mg Premarin daily; Group A received 2.5 mg MPA daily, Group B received 5.0 mg MPA daily, Group C received 5.0 mg MPA daily for days 15-28, Group D received 10.0 mg MPA daily for days 15-28, Group E did not receive MPA.

SOURCE: NDA 20,303, volume 1.40, page 60

Table 3

Incidence of Amenorrhea for at Least Cycles 7 through 13 (6-day window)

	No. of Patients (%) Treatment Group				
Population	A	B	C	D	E
Completed 13 Cycles	(n = 203) 82 (40.4)^{BCDE}	(n = 192) 101 (52.6)^{ACD}	(n = 204) 11 (5.4)^{ABE}	(n = 191) 11 (5.8)^{ABE}	(n = 182) 98 (53.8)^{ACD}
Enrolled	(n = 219) 82 (37.4)^{BCDE}	(n = 213) 101 (47.4)^{ACD}	(n = 233) 11 (4.7)^{ABE}	(n = 226) 11 (4.9)^{ABE}	(n = 202) 98 (48.5)^{ACD}

A,B,C,D,E = Significantly ($p < 0.05$) different from treatment groups a,b,c,d,e, respectively.

All groups received 0.625 mg Premarin daily; Group A received 2.5 mg MPA daily, Group B received 5.0 mg MPA daily, Group C received 5.0 mg MPA daily for days 15-28, Group D received 10.0 mg MPA daily for days 15-28, Group E did not receive MPA.

SOURCE: NDA 20,303, volume 1.40, page 62

Table 4

Incidence of Amenorrhea for at Least Cycles 7 through 13 (2-day window)

	No. of Patients (%) Treatment Group				
Population	A	B	C	D	E
Completed 13 Cycles	(n = 203) 73 (36.0)^{BCDE}	(n = 192) 93 (48.4)^{ACD}	(n = 204) 8 (3.9)^{ABE}	(n = 191) 10 (5.2)^{ABE}	(n = 182) 91 (50.0)^{ACD}
Enrolled	(n = 219) 73 (33.3)^{BCDE}	(n = 213) 93 (43.7)^{ACD}	(n = 233) 8 (3.4)^{ABE}	(n = 226) 10 (4.4)^{ABE}	(n = 202) 91 (45.0)^{ACD}

A,B,C,D,E = Significantly ($p < 0.05$) different from treatment groups a,b,c,d,e, respectively.

All groups received 0.625 mg Premarin daily; Group A received 2.5 mg MPA daily, Group B received 5.0 mg MPA daily, Group C received 5.0 mg MPA daily for days 15-28, Group D received 10.0 mg MPA daily for days 15-28, Group E did not receive MPA.

SOURCE: NDA 20,303, General Correspondence; Labeling Follow-up, January 12, 1995, page 4

In response to issue 3 (the number of discontinuations), per the sponsor, nine subjects in group A (59 patients/15%) compared to four subjects in group B (58 patients/7%) discontinued the study for reasons associated with bleeding (see NDA 20,527/S-006; pages 19-24; Tables 9A and 9B, Primary Reasons For Discontinuation For Patients With 12 or Fewer Treatment Cycles). Although the numbers were low, the " expert panel" felt there was no suggestion that withdrawals for bleeding biased the assessment of amenorrhea in the remaining group. The panel also noted that in subjects who did not complete the study, those in group B had better bleeding profiles in regards to the number of cycles with amenorrhea and in the number of cycles with less bleeding (see NDA 20,527/S-006, page 18; Table 8, Tabulation of Bleeding Data For Patients Who Completed Fewer Than 13 Cycles Of Therapy).

For issue 4, the panel found no disadvantages with respect to safety issues with the Premarin 0.625 mg/MPA 5 mg continuous combined regimen. In summary, at cycle 13, there were no statistically significant differences in lipid parameters, mean changes in glucose levels or insulin concentrations, between patients treated with regimens A and B. Depression was the only drug-related study event with an incidence of ≥2% that showed a statistically significant difference between regimen A (14 patients/4%) and regimen B (28 patients/8%).

There were no differences between regimens A and B in the incidence of breast cancer. However, the clustering of cases in NDA 20,303, especially in the continuous treatment regimens, raised concerns for the FDA reviewer (4 of the 5 cases reported were in the continuous regimens A and B, two each per group). The "expert panel" in their review concluded that data do not exist to demonstrate a difference in the risk of breast cancer between Premarin 0.625 mg/MPA 2.5 or 5 mg. Please see the **Overview of Safety** section of this review for further discussion of the impact of exogenous hormones on the risk of breast cancer.

For issue six, the "expert panel" noted that, in clinical practice, compliance with HRT is enhanced in those individuals who are amenorrheic during therapy. They concluded that since the 5 mg dose of MPA increases the occurrence of amenorrhea, physicians and patients would benefit from the availability of a 5 mg prescribing option (NDA 20,527/S-006, page 7). Please see the **Clinical Practice** section of this review for further discussion.

Reviewer's Comment

The comparative results of a 2-day window analysis with regimens A and B were reviewed by the "expert panel" (Tables 1 thru 8, pages 11 thru 18 in the submission). Based on the data generated, the panel thought that the statistically significant difference seen between regimen A and regimen B in controlling bleeding in later cycles was clinically significant. This reviewer concurs that the differences between regimens A and B are clinically relevant. Most postmenopausal women on HRT do not want to bleed and any bleeding is highly significant, both to the patient and the health provider. Generally, in terms of compliance, subjects participating in clinical trials (generally healthy postmenopausal women counseled and supported to continue the study by frequent follow-up visits) will have a higher level of motivation to continue HRT than might be seen in clinical practice. Having the ability in clinical practice to adjust the dose of continuous combined HRT regimens to the needs of the individual patient offers an opportunity to promote improved compliance and use of HRT. The Agency's statistical reviewer feels that the results reviewed by the" expert panel" presented many hypothesis tests with accompanying p-values with no adjustment for multiple comparisons.

On September 6, 1995 and November 7, 1995, revised amenorrhea labeling was presented for NDA 20,303 which reflected a re-analysis of the original amenorrhea data submitted in NDA 20,303 using a 2-day window following endometrial biopsy as defined in the original protocol. The November 7, 1995 revision included descriptive data on amenorrhea which occurred among all treatment groups with reference to both enrolled (intent-to-treat) and completer (evaluable) populations. This proposed new amenorrhea labeling for Prempro 0.625 mg Premarin/2.5 mg MPA was granted approval.

Attachment II, "Continuous Combined Hormone Replacement Therapy Study: Market Research Study of Physician Use Of 5 mg Progestin In Combination With Estrogen"

The major objectives of this study were (NDA 20,527/S-006, page 43):

- To qualify the level of use of 5 mg progestin/0.625 mg estrogen as part of the continuous-combined hormone replacement therapy (HRT) regimen.
- To determine the frequency of physician prescribing of the 5 mg progestin/0.625 mg estrogen within continuous combined regimens.
- To ascertain reasons for prescribing the 5 mg progestin/0.625 mg estrogen for women on the continuous combined HRT regimen.

The sample for the market research study consisted of either Ob/Gyn or primary care physicians (PCP). The physician list, provided by Wyeth-Ayerst, was selected from the Xponent database compiled by a "service which monitors prescription activity at retail and mail order outlets, and custom project prescriptions." The questionnaire used for the interviews was designed by Wyeth-Ayerst and Hygeia Marketing Associates. Information for this research was gathered through telephone interviews (5 minutes) regarding HRT prescription practices. Physicians interviewed had to be office-based with at least one year but no more than 30 years of post-residency experience and had to be prescribers of HRT for non-hysterectomized, post-menopausal women, and have prescribed continuous combined estrogen and progestin regimens for at least some patients.

The Xponent database contains 149,187 primary care physicians and 35,656 Ob/Gyn physicians. A sample distribution of 50/50 was selected (10,000 PCP/10,000 Ob/Gyn) although the population is split 81% PCP (149,187) and 19% Ob/Gyn (35,656). Fifteen (15) percent of the sample was contacted (1680 PCP and 1380 Ob/Gyn) resulting in a total of 405 eligible interviews completed (210 PCP and 204 Ob/Gyn) which represents only 2 % of the sample selected. Three questionnaire questions addressed the issue of bleeding/spotting problems related to patient compliance:

- For what reason do you prescribe the (most common dose from response to question 1) strength? (question 1 = when you prescribe continuous combined hormone replacement therapy for your patients, which dose of progestin do you most commonly prescribe?)
- Why do you sometimes prescribe 5.0 mg instead of (most common dose from question 1)?
- If a patient on 2.5 mg progestin continuous combined regimen has bleeding you and your patient consider as problematic, what would you do?

Per sponsor, this market survey confirmed (NDA 20,527/S-006, page 45):

- In 93% of the cases when estrogen and progestin are prescribed for daily combined use, the 0.625 mg estrogen/2.5 mg progestin dose was utilized; 6% of the survey sample indicated that they prescribe the 0.625 mg estrogen/5.0 mg progestin dose most commonly for daily combined use.
- For those physicians who prescribed the 0.625 mg estrogen/5.0 mg progestin regimen as their first-line therapy, they cited "less bleeding" in 35% (8/23) of the cases.
- Three out of five physicians who prescribe the 2.5 mg progestin strength most frequently indicated that 5.0 mg progestin was used as part of their continuous combined HRT armamentarium; in 78% of the cases, "bleeding" was the rational behind prescribing the 5.0 mg progestin dose.
- For physicians who did not mention bleeding-related reasons for prescribing the 5.0 mg progestin strength who were aidedly queried as to what they would do for patients with bleeding problems on the 2.5 mg strength, one physician out of five (19%) specified "increase the dose to 5.0 mg of progestin" whereas 6% generally mentioned "increasing the progestin dose" without specifying a dose strength.

In conclusion, the sponsor states: "Although the 5 mg progestin strength in continuous combined hormonal replacement therapy is not used as first-line therapy in the majority of continuous combined HRT regimens, the 5 mg dose of progestin is commonly utilized as an alternative therapy, especially to control bleeding."

Reviewer's Comment

The sponsor concludes from the results of the market research that the data demonstrates a clinical need for the higher Prempro progestin dosage (i.e. 5 mg) in hormone replacement therapy. This reviewer and the biometrics reviewer agree that for this review of the market research study the main concerns were bias and the representativeness of these results to the whole population. Per the biometrics review, four possible sources of bias were identified. In summary, the first possible source of bias is the database used as the source of the sample; the second possible source of bias is the stratified sampling used within each of the 2 speciality groups; the third possible source of bias are the four qualifying questions used to limit the respondents to a particular subset of interest which results in a selective sample which may introduce bias unless these criteria are considered in the interpretation of the results; and the final source of bias in this market research study is non-response (see Statistical Review and Evaluation of Non-clinical Studies for a complete review).

Per the Statistical Review, the uncorrected estimate of the percent of physicians who prescribed the 2.5 mg dose most commonly and who would mention bleeding as a reason for sometimes prescribing the 5.0 mg dose was 4-5 percentage points higher than the range of estimates calculated using the weighted approach for the stratification of the sample.

From a clinical perspective any unexplained bleeding is highly significant to postmenopausal women and requires prompt, appropriate endometrial evaluation. For those patients with negative endometrial evaluations who desire to continue HRT, added benefit may be gained from less bleeding with the use of a higher progestin dose.

Overview of Efficacy

Primary Efficacy Variable

For the primary efficacy variable of prevention of endometrial hyperplasia, the primary clinical efficacy and safety database for this NDA is by reference to the large-scale, multicenter, randomized, placebo-controlled pivotal trial for NDA 20,303 (Premarin and MPA separate tablets). NDA 20,303 provided evidence that concomitant MPA reduces the risk of endometrial hyperplasia induced by treatment with unopposed Premarin from a 1-year incidence of 8% (20% when focal hyperplasia was included) to 1% or less, with $p < 0.001$ for all between-group comparisons of combination therapy versus unopposed Premarin. This effect was statistically significant, clinically significant, and similar in magnitude for the lower (2.5 mg) and higher (5 mg) MPA doses and for both the sequential and continuous MPA regimens administered with Premarin 0.625 mg daily by oral administration.

Endometrial hyperplasia is clinically important in part because it is associated with an increased risk of endometrial cancer. In a published article reporting the results of study 713B-300 (NDA 20,303), Woodruff and Pickar concluded that all four medroxyprogesterone acetate regimens used with conjugated estrogens in the study effectively reduced the incidence of endometrial hyperplasia associated with the use of estrogens taken alone (Woodruff, JD, and Pickar, JH, Incidence of endometrial hyperplasia in postmenopausal women taking conjugated estrogens (Premarin) with medroxyprogesterone acetate or conjugated estrogens alone, American Journal of Obstetrics and Gynecology, volume 170, number 5, part 1, May 1994, pages 1213 - 1223).

Secondary Efficacy Variables

Menopausal vasomotor symptoms and vaginal bleeding episodes were recorded on daily diary cards by the patients throughout the study (Protocol No. 713B-300 only). The overall results of vasomotor symptomatology analysis provide evidence that concomitant MPA treatment does not reduce the efficacy of Premarin in relieving moderate to severe vasomotor symptoms associated with menopause (MO review dated 12/30/94, page 34).

The overall incidence of "irregular bleeding" and "irregular spotting" was similar with both sequential regimens. In the continuous regimens, group A (0.625 mg estrogen/2.5 mg MPA) had a higher incidence of "irregular bleeding" (22.3%) and "irregular spotting" (16.2%) than group B (0.625 mg estrogen/5.0 mg MPA) at 12.7 % and 14.4% of cycles, respectively.

Overview of Safety

In NDA 20,303, all treatment regimens were well tolerated with no deaths, few hospitalizations, few malignancies and few serious adverse events, including cardiovascular events, occurring during the study. Breast cancer developed in 5 subjects during the study drug treatment (2 each in regimens A and B, 1 in group C). These findings are consistent with the expected background incidence in the relevant age groups in the general population (2 to 3 per 1000 women annually (Miller BA, Reis LAG, Hankey BF, Kosary CL, Edward BK, editors. Cancer statistics review: 1973-1989, National Cancer Institute. NIH Pub. No. 92-2789, 1992). Per the Medical Officer's Review, "Although there were no statistically significant differences in breast cancer incidence between treatment groups, the clustering of cases in the Premarin/MPA groups, (especially in the continuous treatment regimen) raises concern that concomitant progestin may exacerbate the increment in breast cancer risk that has repeatedly been observed with prolonged unopposed estrogen treatment".

Reviewer's Comment

The impact of exogenous hormones on the risk of breast cancer has been the focus of considerable interest in recent years. There have been many cohort and case-controlled studies of women using HRT and these have yielded inconsistent findings. A summary of some of the literature findings is listed below:

♦ A large multicenter study by Newcomb in 1995, demonstrated that users of hormone replacement therapy had a relative risk of breast cancer that was similar to that in women using estrogens alone or in women who had never used postmenopausal hormones and was not significantly different from 1.0 (Newcomb PA, Longnecker MP, Storer BE, Mittendorf R, Baron J, Clapp RW et al. Long-term hormone replacement therapy and risk of breast cancer in postmenopausal women. Am J Epidemiol 1995; 142(8):788-95).

♦A prospective, randomized, 22-year study on breast cancer in continuously hospitalized postmenopausal women on HRT or placebo reported by Nachtigall in 1992 showed an overall incidence of breast cancer in the women who had never taken HRT to be 11.5% (six of 52), whereas no (0 of 116) breast cancers developed in the women who had ever taken HRT ($p < .01$) (Nachtigall MJ, Smilen SW, Nachtigall RD et al. Incidence of breast cancer in a 22-year study of women receiving estrogen-progestin replacement therapy. Obstet Gynecol 1992; 80:827-830).

♦In a population-based case-controlled investigation by Stanford reported in 1995, women (>1,000) who used estrogen-progestin HRT for 8 or more years, compared to nonusers, had a reduced risk of breast cancer (of borderline significance with relative odds = 0.4, confidence interval 0.2 to 1.0) (Stanford JL, Weiss NS, Voigt LF et al. Combined estrogen and progestin hormone replacement therapy in relation to risk of breast cancer in middle-aged women. JAMA 1995; 274:137-42).

♦The 1995 report from the Nurses' Health Study representing 725,550 person-years of follow-up, documented 1,935 cases of breast cancer (Colditz GA, Hankinson SE, Hunter DJ, Willett WC, Manson JE, Stampfer MS et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. NEJM 1995; 332:1589-93). The analysis revealed that the risk of breast cancer was significantly increased among women who were currently using estrogen alone (relative risk of 1.32) or estrogen plus progestin (relative risk of 1.41) as compared with postmenopausal women who had never used hormones. The adjusted relative risk for current-users was 1.46 for 5 to 9 years of use, and 1.46 for 10 or more years of use, disturbing with its findings of an increased risk in current users (greater among women aged 60 to 64

years old, 1.71 relative risk). Women who had used estrogen in the past (even for 10 or more years) were not at risk of developing breast cancer.

♦The 1997 report by the Collaborative Group on Hormonal Factors in Breast Cancer, analysis and writing committee in the UK, representing a mega-analysis of data from 51 epidemiological studies in 21 countries with individual data on 52,705 women with breast cancer and 108,411 women without breast cancer (main analysis based on 53,865 postmenopausal women with known age at menopause, of whom 17,830 [33%] had used HRT at some time) found that the increase in the relative risk of breast cancer for each year of use of HRT among current users or those who ceased use 1-4 years before diagnosis was 1.023. For current or recent users with a duration of use of 5 or more years, the relative risk of having breast cancer diagnosed was 1.35. The only factors that seemed to modify the effect of HRT in current or recent users were a woman's weight and her body-mass index (Collaborative Group on Hormonal Factors in Breast Cancer, analysis and writing committee. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. The Lancet 1997; 350: 1047-1059). The effect of long durations of current or recent use were more pronounced for women of low body-mass index than for those of high body-mass index, and the trend of increasing relative risk with decreasing weight or body-mass was highly significant (0.004 and 0.0001, respectively). Per the report, insufficient data were available to permit reliable conclusions about the effects of different hormonal preparations on breast cancer risk (for the 39% of the study population with information on hormonal regimens, 80% had used mostly estrogen alone). Additionally, the report shows that 5 or more years after cessation of HRT use there was no significant excess of breast cancer overall (relative risk 1.07) or among women who had used HRT for 5 years or longer (relative risk 0.92).

In summary, the impact of exogenous hormones on the risk of breast cancer has been the focus of considerable interest in recent years as the use of exogenous hormones has increased. Many cohort and case-controlled studies of women using HRT have been conducted. In addition, several meta-analyses have been published to attempt to clarify these results. Overall, these meta-analysis suggest that the risk of developing breast cancer with HRT use may not increase with short-term use (less than 5 years). With long-term use, greater than 10 years , there may be a slightly increased risk of developing breast cancer but other biological factors (ie, family history, diet, smoking, etc) must be considered.

When NDA 20,303 was approved in 1994, the sponsor agreed to conduct a comprehensive Phase IV investigation of breast cancer risk in users and non-users of the NDA regimens. It was recommended that a large-scale, case-control U.S. study would be the most feasible approach to evaluate differences between Prempro versus Premphase. In a recent letter to the Agency dated September 25, 1997, the sponsor requested the Agency's concurrence that two large ongoing prospective studies receiving Wyeth-Ayerst's support would fulfill the Phase IV commitments to conduct the breast cancer investigation. The NIH's "Women's Health Initiative" (WHI) nine year observational study to include 100,000 women and clinical trial with a projected enrollment of 68,000 women, 27,500 who will be randomized to hormone replacement therapy is designed to compare all replacement therapy with placebo; the Medical Research Council's "Women's International Study of long-Duration Oestrogen after Menopause" (WISDOM) eleven year placebo-controlled clinical trial has a projected enrollment of 34,000 women. Wyeth-Ayerst has committed to support both the WHI and WISDOM trials by providing active drug product and placebo. The sponsor concluded that the proposed Phase IV protocol submitted would draw from overlapping patient populations as the two prospective clinical trials and would not likely yield results different from those anticipated from WHI and WISDOM. The Agency completed a review of the September 25, 1997 submission and concluded that Wyeth-Ayerst's support for these two prospective studies would fulfill their Phase IV commitment. The sponsor was informed on November 12, 1997 that conduct of the previously discussed Phase IV case-control study was not necessary.

Clinical Practice

Per the sponsor, justification for requesting approval of a 0.625 mg CE/5 mg PMA tablet stems from a request to supply an additional 2.5 mg MPA tablet for continuous use along with Prempro (0.625mg CE/2.5 mg MPA) for the Women's Health Initiative (WHI) so that women who continue to spot or bleed, in this study, while taking Prempro could be offered additional progestin. In the supplemental application cover letter, the sponsor indicates that " a larger number of women than anticipated continued to bleed or spot after 6 months and even after 1 year, and the continued bleeding affects compliance". The WHI Council, meeting on August 2, 1996, resolved that women who continue spotting or bleeding on Premarin 0.625 mg plus Cycrin 2.5 mg continuous may be offered an additional 2.5 mg of continuous Cycrin for the duration of the study (IND 20,527/S-006, page 34). Because the administration of open-label Cycrin would unfortunately involves unblinding the study gynecologist and the participant, the WHI Council asked Wyeth-Ayerst its plans to produce a combined Premarin 0.625 mg/5 mgMPA tablet or its ability to make such a combination tablet available for study purposes.

Bleeding has been cited as one of the primary reasons for discontinuing therapy. Because withdrawal bleeding occurs in 80% to 90% of patients on cyclic combined hormonal replacement therapy a most attractive aspect of combined continuous therapy is its absence. Several studies have reported compliance ranging from 80% to 100% in patients on continuous hormonal replacement therapy. In general, there is a high incidence of irregular bleeding in the first 3 months of continuous therapy; however, most patients are amenorrheic by 12 months of therapy. Yancy et al. compared 10 mg MPA versus 5 mg MPA and found that 92% of patients on 10 mg were amenorrheic versus 73% of patients on 5 mg (Yancy MK, Stone IK, Hannan CJ et al. Serum lipids and lipoproteins in continuous or cyclic medroxyprogesterone acetate treatment in post-menopausal women treated with conjugated estrogens. Fertil Steril 1990;54:778-82) . In a study by Prough at al., 12.5 % of patients on 2.5 mg MPA were still bleeding at 9 months (Prough SG, Aksel S, Weibe H, Sheperd J. Continuous estrogen/progestin therapy in menopause. Am J Obstet Gynecol 1987;157:1449-53). Weinstein et al. compared 2.5 mg with 5 mg MPA and found no differences in bleeding between groups; 82 % of patients were amenorrheic at 40 weeks (Weinstein L, Bewtra C, Gallagher JC. Evaluation of a continuous combined low dose regimen of estrogen for treatment of the menopausal patient. Am J Obstet Gynecol 1990;162:1534-42).

The importance in clinical practice of being able to adjust the dose of continuous combined hormone replacement therapy of individual patients is noteworthy.

Labeling Review

The proposed annotated labeling for Prempro was reviewed with reference to the approved labeling for PREMPRO (combined tablets, NDA 20,527). A labeling meeting was held on November 13, 1997; see meeting minutes attached.

Reviewer's Assessment

This NDA 20,527 Efficacy Supplement presents information in support of a continuous combined dosing regimen of 0.625 mg conjugated estrogens/5 mg medroxyprogesterone acetate for Prempro Tablets. Data from the original NDA 20,303 for conjugated estrogens tablets and medroxyprogesterone acetate tablets, approved on December 31, 1994, is referred to in this submission (approval was granted for the 0.625 mg conjugated estrogens/2.5 mg MPA continuous dosing regimen and the 0.625 mg CE/5 mg MPA sequential dosing regimen). In addition, recommendations of an "expert panel" and information from market research is also submitted.

It is well established that the adverse effects of the cessation of ovarian estrogen secretion in postmenopausal women can be ameliorated or reversed by estrogen replacement therapy. Importantly, adding a progestin (5 mg) to estrogen replacement therapy for at least 10 days per cycle, or 2.5 mg or 5 mg continuously, effectively reduces the risk of

endometrial hyperplasia and subsequently endometrial cancer.

Compliance with hormone replacement therapy is medically important in several respects. The recently completed 3-year, multicenter, randomized, double-blind, placebo-controlled Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial demonstrated, in addition to the effects of hormone replacement therapy on endometrial histology in postmenopausal women, that oral estrogen taken alone or with progestin (MPA or micronized progesterone) is associated with improved lipoprotein and lower fibrinogen levels compared with placebo that is likely to be clinically significant (Writing Group for the PEPI Trial. PEPI Effects of estrogen/progestin regimens of heart disease risk factors in postmenopausal women. JAMA 1995;273(3):199-208). Although, each active treatment regimen was associated with a significantly greater increment in mean HDL-C levels than placebo, women assigned to CEE alone or CEE with micronized progesterone (MP) had significantly greater HDL-C elevations than women assigned to CEE with cyclic or continuous MPA. This loss with regards to HDL-C must be balanced with the rate of adenomatous or atypical endometrial hyperplasia with unopposed estrogen for women with a uterus. Additionally, data from PEPI show that estrogen use, on average, increases bone mineral density (BMD, a potent predictor of fracture risk) in the spine and hip during the 3-years of therapy. Women assigned to CEE plus continuous MPA had significantly greater increases in spinal BMD (5%) than those assigned to other treatment groups (average of 3.8%). However, analysis of the adherent participants suggests that combined estrogen/progestin treatment is not superior to unopposed estrogen in maintaining or increasing BMD at these sites.

Given these positive findings in regards to osteoporosis prevention and the reduction of cardiovascular risk in the postmenopausal women, compliance with HRT becomes a medical issue with regards to the ongoing health of the postmenopausal woman. The use of continuous combined hormonal regimens to achieve amenorrhea, in comparison to cyclic regimens, appears to be attractive to the postmenopausal patient population and has been shown to increase patient acceptance. The data available in NDA 20,303 and this submission, NDA 20,527/S-006, demonstrate a clinically important difference in the incidence of spotting and bleeding between regimen A and regimen B. The risk/benefit balance for a Prempro dosage form combining Premarin 0.625 mg and 5.0 mg MPA appears acceptable.

Reviewer's Comment

Estrogens and progestins have several important uses but also risks. The lowest possible effective dose should be used at all times. For the treatment of moderate-to-severe vasomotor symptoms, vulval and vaginal atrophy associated with menopause, and the prevention of osteoporosis, patients should be started at the lowest effective daily dose of Prempro (Premarin 0.625 mg/MPA 2.5 mg), monitored closely for side effects, and appropriately evaluated when necessary.

Recommendations for Regulatory Action

This NDA Efficacy Supplement is recommended for approval. The previously noted labeling changes will be communicated to the sponsor in a regulatory letter.

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

1/5/98

Attachment: Meeting Minutes, November 13, 1997
cc: NDA 20,527 Division File
HFD-580/DMoore/HJolson/TvanderVlugt