CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-527/S-006

PHARMACOLOGY REVIEW(S)

Moore

N20527.S006 FEB 19 1997

2-18-1997

NDA 20-527

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

Submission dated: 1-8-1997 Received at HFD-580: 1-9-1997

Pharmacology review of NDA 20-527
S-006

Drug: Prempro (conjugated estrogens/medroxyprogesterone acetate) tablets

Route of administration: oral

Tablet strength: 0.625 mg conjugated estrogens (CE)/5 mg medroxyprogesterone acetate (MPA)

Proposed indications: vasomotor symptoms and estrogen deficiency osteoporosis.

Under NDA 20-303 dated 12-22-1992, the sponsor had sought approval of the following 2 continuous and one sequential dosing regimens as shown below:

Conjugated estrogens		Medroxyprogesterone acetate
0.625 mg, days 1-28	+	2.5 mg, days 1-28
0.625 mg, days 1-28	+	5.0 mg, days 1-28
0.625 mg, days 1-28	+	5.0 mg, days 15-28

Although NDA was approved on 12-30-1994, Agency did not approve the continuous combined 28-day regimen of 0.625 mg CE/5 mg MPA. Agency's rationale was that the efficacy results, in terms of treating vasomotor symptoms and preventing endometrial hyperplasia, were indistinguishable for the 0.625 mg CE/2.5 mg MPA continuous combined regimen vs the continuous combined 0.625 mg CE/5.0 mg MPA regimen.

The sponsor has now submitted evidence that use of 0.0625 mg CE/5 mg MPA combined regimen was considered better in controlling bleeding and improving compliance in a study conducted by NIH

under the Women's Health Initiative program. Additionally sponsor has included a report by a panel of experts entitled "Recommendations of Expert Consultants on the Premarin 0.625 mg/MPA 5 mg 28-day continuous regimen". The report concluded that there was no clinically important differences in safety of 0.625 mg CE/5 mg MPA combination regimen vs 0.625 mg CE/2.5 mg MPA combination regimen. However, findings with respect to amenorrhea in the group taking 0.625 mg Premarin and 5 mg MPA vs 0.625 mg Premarin and 2.5 mg MPA were considered clinically meaningful.

Pharmacology had no objection and had recommended approval of all the three then proposed CE/MPA combination regimens under NDA 20-303 on 6-7-1993 (copy of review appended). The sponsor has complied with the Pharmacology comments that the occurrence of MPA-induced dose-related increase in pancreatic islet cell tumors (adenomas and carcinomas) in the rat carcinogenicity study be included in the labeling.

Labeling: Draft labeling is similar to that for sponsor's approved NDA 20-303 for CE/MPA.

Recommendations: Both Premarin and medroxyprogesterone acetate are FDA approved drugs for doses to be used in the proposed combination regimen. Pharmacology had recommended approval 0.625 mg CE/5.0 mg MPA combination continuous dosing regimen under NDA 20-303 and has no objection to its approval under NDA 20-527 for the proposed indications.

2/19/97

Krishan L. Raheja, D.V.M., Ph.D

Original NDA 20-527 S-006
HFD-345
HFD-580
HFD-580/A.Jordan
HFD-580/K.Raheja, 2-18-1997, N20527.S006

2/19

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-527/S-006

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Non-Clinical Studies

Date: AUG 21 1997

NDA #: 20-527 / S-006

Applicant: Wyeth-Ayerst

Name of Drug: Prempro Tablets (conjugated estrogens / medroxyprogesterone acetate)

Indication: Treatment of vasomotor symptoms and endometrial hyperplasia in hormone replacement therapy (HRT)

Documents Reviewed: Supplement Number S006 (Non-clinical)

Statistical Reviewer: Kate Meaker, M.S. (HFD-715)

Medical Input: Theresa van der Vlugt, M. D. (HFD-580)

Summary of Studies

Clinical study data for two dose regimens of Prempro were submitted in an original NDA number 20-303. In December 1994, NDA 20-303 was approved for the 0.625 mg CE/2.5 mg MPA dose, but not for the 0.625 mg CE/5 mg MPA dose. The purpose of Supplement number S-006 is to provide additional, non-clinical information in support of the 0.625 mg CE/2.5 mg MPA dose. A non-clinical market research study, "Continuous Combined Hormone Replacement Therapy Study: Market Research of Physician Use of 5 mg Progestin in Combination with Estrogen," was submitted with this supplement. This market research study is the only study for statistical review. The purpose of this statistical review is to assist the medical officer in assessing how relevant the information presented from the market research study is to the decision on approving the 0.625 mg CE/5 mg MPA dose.

The supplement also included a report from an expert panel who had reviewed the same clinical study results which had been submitted under NDA 20-303. Statistical review of this report is not necessary because the report included only comments of a medical nature and the statistical analyses had been reviewed by Lee-Ping Pian (HFD-715) in December 1994. However, this reviewer feels it is worth noting that the results reviewed by the expert panel presented many hypothesis tests with accompanying p-values with no adjustment for multiple tests.

Background

The sample for the market research study consisted of physicians who were either Ob/Gyns or Primary Care Physicians (PCP). It was selected from the Xponent database which is independent of Wyeth-Ayerst. The Xponent database is compiled by "a service which monitors prescription activity at retail and mail order outlets, and custom project prescriptions, generated by over individual prescribers every month" (pg 90). There are 149,187 Primary Care Physicians and 35,656 Ob/Gyn physicians contained in this database.

There were 2 stages in the sample selection process. The first, stratification, specified that half the sample would be from each of the 2 specialty groups. Within each specialty, systematic sampling was used to ensure equal representation for physicians from all levels of HRT prescription frequency. This was accomplished by ordering the physicians within each specialty by the number of HRT prescriptions written, then dividing each specialty group into quintiles. Quintile 1 contains physicians who wrote the fewest HRT prescriptions, and quintile 5 contains those who wrote the most HRT prescriptions, within each specialty. Starting at a random subject, every nth subject was selected from the ordered list. The resulting sample contained approximately 20% in each quintile within each specialty.

Subjects were contacted via phone for a short (5 minutes) interview regarding their HRT prescription practices. There were 4 eligibility criteria for subjects. All subjects had to be office-based PCP or Ob/Gyn physicians with at least 1 year but no more than 30 years of post-residency experience. They must have been prescribers of HRT for non-hysterectomized, post-menopausal women, and have prescribed continuous combined (estrogen and progestin) regimens for at least some patients. After the eligibility criteria had been confirmed, subjects were asked about the progestin dose(s) they prescribed for continuous combined HRT regimens.

The objectives of the market research study, as stated by the applicant (pg. 43), were:

- To quantify 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 the continuous combined regimens.
- To ascertain reasons for prescribing 5 mg progestin/0.625 mg estrogen for women on the continuous combined HRT regimen.

The main issue for the medical officer is bleeding/spotting problems which have been related to patient compliance. The survey of physicians did not address this directly but does provide some information. There were 2 unaided[1] questions (Q1a, Q2a) regarding reasons for prescribing different progestin doses in continuous combined HRT in which physicians mentioned bleeding. If the physician did not specifically mention bleeding-related reasons for prescribing the 5.0 mg dose in the unaided portion of the questionnaire, then a direct question (Q4) about this was asked. These three questions will be the focus of this review.

[1] An unaided, or open-ended, question does not provide a list of possible answers or prompt the respondent toward a desired topic.

Sample Disposition

Only 15% of the sample was contacted, resulting in completed eligible interviews for only 2% of the sample. Completion rates were similar for the 2 specialty groups overall (Table 1). Return rates were lower for quintiles 1 and 2 within both specialty groups than for the higher quintiles (Table 2 - see next page). Subjects in quintile 1 were more likely to be ineligible than those in higher quintiles, which may be logical since 2 of the criteria refer to HRT prescription practices. Subjects in quintile 2 were simply less likely to be contacted, an unexplained fluctuation.

Table 1: Sample Selection and Disposition by Specialty

	Total	Primary Care Physicians (PCP)		Ob/Gyn	
	N	N	% of Total	N	% of Total
Xponent Database	184843	149187	80.7%	35656	19.3%
Sample	20000	10000	50.0	10000	50.0
Contacted	3060	1680	54.9	1380	45.1
Contacted - Incomplete or Refused to Participate	2494	1368	54.9	1126	45.1
Eliminated on Eligibility Questions (D1-D4)	162	111	68.5	51	31.5
Eligible Completed Interviews	405	201	49.6	204	50.4

Source: Letter from applicant dated 6/2/97

Table 2: Sample Selection and Disposition by Quintile Within Specialty

Specialty	**Primary Care Physicians (PCP)** (N=149,187 in Xponent Database) Total Sample = 10,000					**Ob/Gyn** (N=35,656 in Xponent Database) Total Sample = 10,000				
Quintiles	1	2	3	4	5	1	2	3	4	5
Sample	2032	1967	2055	1950	1996	1983	1973	2037	2002	2005
(percent of total sample within specialty)	(20.3)	(19.7)	(20.6)	(19.5)	(20.0)	(19.8)	(19.7)	(20.4)	(20.0)	(20.0)
Percent of sample within quin./specialty	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Contacted	299	261	347	400	373	296	218	275	297	295
Percent of sample within quin./specialty	14.7	13.3	16.9	20.5	18.7	14.9	11.0	13.5	14.8	14.7
Contacted - Incomplete or Refused to Participate	226	224	280	330	308	256	171	211	246	242
Percent of sample within quin./specialty	11.1	11.4	13.6	16.9	15.4	12.9	8.7	10.4	12.3	12.1
Eliminated on Eligibility Questions (D1-D4)	53	15	15	13	15	27	8	4	3	9
Percent of sample within quin./specialty	2.6	0.8	0.7	0.7	0.8	1.4	0.4	0.2	0.1	0.4
Eligible Completed Interviews	20	22	52	57	50	13	39	60	48	44
Percent of sample within quin./specialty	1.0	1.1	2.5	2.9	2.5	0.7	2.0	2.9	2.4	2.2

Source: Letter from applicant dated 6/2/97

Table 2 does not list the Xponent database by quintiles because this information was not available. The assigned quintiles categories were recorded with the sample when it was selected. The method of determining and assigning the quintiles for the database has been changed since the sample was selected, and the figures for the database could not be reproduced.

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ON ORIGINAL

Applicant's Analysis

The applicant's analysis of the market research study consisted of cross-tabulations of each question by characteristics of the physicians who responded (specialty, level of prescribing within specialty, years in practice, and most common dose of progestin when prescribing continuous combined HRT). The results for questions 1A, 2A, and 4, along with the applicant's conclusions, appear below.

In the sampling process, physicians within each specialty were assigned to one of 5 quintiles, with approximately 20% in each category within each specialty and within the total sample. The return rate was lower in quintiles 1 and 2 for both specialties (see Table 2). When the data were tabulated, the 5 quintiles were collapsed to 2 categories: Low = quintiles 1-3; High = quintiles 4-5. The Low category included 60.2% of the total sample but only 50.9% of the completed interviews. The High category included 39.8% of the total sample and 49.1% of the returns. Thus the Low/High split defined after the data was collected is approximately a 50/50 split of the returns but is not representative of the original sample.

Table 3: Q1A For what reason do you prescribe the (most common dose from Q1) strength?
(multiple responses permitted per physician)

		Primary Care Physicians			Ob/Gyn			Most Common Dose			
Q1A	Total	Total	High	Low	Total	High	Low	2.5 mg	5.0 mg	10 mg	Other
Less Bleeding (% of total responders)	39 (10%)	20 (10%)	9 (9%)	11 (11%)	19 (9%)	11 (12%)	8 (7%)	29 (8%)	8 (35%)	1 (20%)	1 (50%)
Total Responders	405	201	102	99	204	94	110	375	23	5	2

Source: Table 6-1, pg. 64-66

The applicant concluded that "Among 23 physicians who prescribed the 5 mg progestin dose most commonly, 35% cited 'less bleeding' as their primary reason." (pg. 37). It should be noted that Question 1 refers only to when prescribing continuous combined HRT, not cyclic regimens.

Table 4: Q2A Why do you sometimes prescribe 5.0 mg instead of (most common dose from Q1)?
(multiple responses permitted per physician)

		Primary Care Physicians			Ob/Gyn			Most Common Dose			
Q2A	Total	Total	High	Low	Total	High	Low	2.5 mg	5.0 mg	10 mg	Other
Bleeding (% of total responders)	176 (78%)	73 (71%)	45 (75%)	28 (65%)	103 (83%)	48 (81%)	55 (85%)	176 (79%)	--	0 (0%)	0 (0%)
Total Responders	227	103	60	43	124	59	65	224	--	2	1

Source: Table 10-1, pg. 71-72

The applicant states that "Among the 375 physicians who prescribed the 2.5 mg dose most commonly, 227 (56%) [sic] said that they also prescribed the 5 mg progestin dose for continuous combined HRT. For 78% [sic] of these prescribers, control of a bleeding problem was the main reason for prescribing 5 mg progestin." (pg 37).

The figures reported by the applicant in the conclusions (pg. 37) do not match the figures presented in the tables. Using the figures from Table 10-1, the actual values are 224 (60%) of the 375 physicians who prescribed the 2.5 mg dose most commonly said that they also prescribed the 5 mg progestin dose for continuous combined HRT, and for 176 (79%) of these 224 prescribers, control of a bleeding problem was the main reason for prescribing 5 mg progestin. As in question 1, question 2 specifically refers to continuous combined HRT regimens.

Table 5: Q4 If a patient on 2.5 mg progestin continuous combined regimen has bleeding you or your patient consider as problematic, what would you do?
(Only asked during the interview if bleeding-related reasons were not mentioned in Q1a or Q2a for the 5.0 mg dose.)
Multiple responses permitted per physician.

		Primary Care Physicians			Ob/Gyn			Most Common Dose			
Q4	Total	Total	High	Low	Total	High	Low	2.5 mg	5.0 mg	10 mg	Other
Use 5.0 mg dose to resolve bleeding (% of total responders)	43 (19%)	30 (23%)	14 (24%)	16 (23%)	13 (13%)	6 (13%)	7 (13%)	37 (18%)	5 (31%)	0 (0%)	1 (50%)
Increase progestin dose (% of total responders)	13 (6%)	11 (9%)	6 (10%)	5 (7%)	2 (2%)	0 (0%)	2 (4%)	10 (5%)	3 (19%)	0 (0%)	0 (0%)
Total Responders	227	128	58	70	99	45	54	204	16	5	2

Source: Table 18-1, pg. 81-84

Only physicians who did not mention bleeding-related reasons for prescribing the 5.0 mg dose in the unaided questions (1A and 2A) were asked Question 4. The applicant concluded that "one physician out of five (19%) specified 'to increase the dose to 5 mg of progestin' whereas 6% generally mentioned 'increasing the progestin does' without specifying a dose strength." (pg 45).

Reviewer's Analysis

The original data for the market research study were not available for analysis by this reviewer. Only the data provided in the applicant's tables and subsequent letter (6/2/97) were used for this review. The focus of the review was on 3 questions (Q1A, Q2A, and Q4) regarding bleeding-related issues with respect to the 5.0 mg progestin dose in a continuous combined HRT regimen.

This reviewer and the medical officer agreed that for this review of a non-clinical study, the main concern was bias and the representativeness of these results to the whole population. Four possible sources of bias were identified and investigated by this reviewer.

The first possible source of bias is the database used as the source of the sample. The applicant assumes that the sample is representative of the whole population of physicians in these 2 specialties (PCP and OB/Gyns) because it was randomly selected from the Xponent database. In discussions with the applicant (telecon 6/17/97) they assured us that the Xponent database is a comprehensive database of prescribing physicians and is generally accepted in the industry as being representative of this population. Beyond this assurance from the applicant, the unbiasedness of the random sample cannot be confirmed. If the assumption that the Xponent database is representative of all PCP/Ob/Gyn physicians, then the random sampling protects against selection bias.

The next issue with respect to possible bias is the stratified sampling used within each of the 2 specialty groups. If the selection quotas for each strata match the population distribution, then the use of unweighted estimates is not a concern. In this study, the population is split 81% PCP and 19% Ob/Gyns, but the sample distribution is 50/50. Therefore the sample is not representative of the total population of interest. It is possible to correct for this unbalancedness by weighting the results to reflect the population distribution. This was not done in the tabulations presented by the applicant, but enough information was provided for this reviewer to reanalyze the results with appropriate weighting. Those results are presented after discussion of additional sources of possible bias.

The survey began with four qualifying questions which were used to limit the respondents to a particular subset of interest among PCP/Ob Gyn physicians. The eligibility questions, with qualifying answers in parentheses, were:

D1. Is the doctor an office-based GP/FP, IM, Ob/Gyn, or Gyn? (Yes)
D2. How many years in practice post-residency? (1 to 30 years)
D3. Prescribes hormone replacement therapy for non-hysterectomized, post-menopausal patients? (Yes)
D4. Prescribes Continuous Combined or both Cyclic and Continuous Combined regimens for HRT? (Yes)

These questions result in a selective sample which may introduce bias unless these criteria are considered in the interpretation of the results. All conclusions should be viewed with respect to the prescribing decisions of PCP/Ob Gyn physicians who meet these criteria, not the entire population of PCP/Ob Gyn physicians. There is not enough information provided about the full population to assess what impact these inclusion criteria might have on the conclusions.

The final source of possible bias in this market research study is non-response. This market research study had a very low response rate (2% of total sample), and the rate was lower in quintiles 1 and 2 than in the upper 3 quintiles. In essence, it is necessary to assume that the subjects who responded (2%) do not differ in their responses from the other 98% of the sample who were either not contacted (85% of sample) or did not complete the survey (12.5%). It is also necessary to assume that the 15% of the sample who were contacted are representative of the total sample of 20,000 physicians originally selected. The generalizability of the results from this survey depend on these assumptions. The impact of non-response cannot be determined from the information available because the observed data do not provide any information about the unobserved subjects.

Reweighting For Stratified Sampling

The applicant's tables present unweighted estimates which do not account for the population distribution across the PCP / Ob Gyn strata. In order to calculate population estimates which correct for the unbalanced stratified sampling, it is necessary to be able to identify how many of the total responders for each question and how many of those who mentioned bleeding are in each of the strata. Sufficient information was available from the tables to do this for the 3 bleeding-related questions. The population estimates are based on reweighting the data to reflect the population distribution.

Q1A: For what reason do you prescribe the (most common dose from Q1) strength?

The subgroup of interest for this question was the 23 physicians who said the 5.0 mg progestin dose was the dose they prescribed most often for continuous combined HRT. Among these, 8 mentioned less bleeding as the reason. The exact population estimate for this question could not be calculated because the exact split of these 8 responders into the PCP / Ob Gyn strata was not known, but it is possible to calculate a range by considering the maximum possible split into either group. The most that could have been in the Ob Gyn group was 5, which resulted in an overall population estimate of 32.7% of physicians in these 2 specialties who prescribed the 5 mg progestin dose most commonly would cite 'less bleeding' as their primary reason. The maximum that could have been in the PCP group was 8, which gave an overall population estimate of 35.9%. The unweighted estimate from the applicant's analysis was 34.8%, which falls between the range %. Therefore the impact of bias is small for this question.

Q2A: Why do you sometimes prescribe 5.0 mg instead of (most common dose from Q1)?

There were 224 physicians who said the 2.5 mg dose was their most common dose and that they also sometimes prescribe the 5.0 mg dose of progestin. Among these, 176 listed bleeding as a reason for prescribing the 5.0 mg dose. For this question, the split between the PCP / Ob Gyn strata for the 176 who mentioned bleeding was given, but the exact split for the 224 responders was not. As in Q1A, it was possible to calculate a range for the weighted estimate by looking at the maximum number out of the 224 who could be in either group. From the applicant's Table 8-1, the maximum number in the PCP group was 103, and the maximum in the Ob Gyn group was 124. Using these limits, the range for the weighted estimate for the population was 73.6% to 74.9% of physicians who prescribe the 2.5 mg dose most commonly would mention bleeding as a reason for sometimes prescribing the 5.0 mg dose. The unweighted estimate from the applicant's analysis was 78.6%, which exceeds the upper limit of this range. For this question, the bias of using unweighted estimates does impact the results.

Q4: If a patient on 2.5 mg progestin continuous combined regimen has bleeding you or your patient consider as problematic, what would you do?

This question was only asked if the physician did not mention bleeding-related reasons for the 5.0 mg dose in the unaided questions (1a and 2a). There were 227 total responders for this question, of whom 43 listed using the 5.0 mg dose for problematic bleeding. The distribution of these subjects across the 2 specialty groups was provided (applicant's Table 18-1), so an exact estimate could be calculated. The weighted estimate was 21.4% of physicians in these specialties would mention using a 5.0 mg dose of progestin to resolve problematic bleeding. This is slightly higher than the unweighted estimate (18.9%) from the applicant's analysis.

Conclusions

The generalizability of the results of this market research study to the population of primary care and Ob/Gyn physicians depends on how well the subjects who had completed interviews reflect the whole population. There are several sources of possible bias which could introduce error and reduce the validity of making conclusions about the whole population based on the results of this survey.

The use of a randomized sample from a large, representative database protects against one source of bias, assuming the applicant's assertions about the Xponent database are true. The impact of two other possible sources, narrowing the sample to a select group via eligibility questions and non-response, cannot be assessed because the observed data do not provide information on the unobserved data.

The last source of bias, the use of unweighted estimates, did show an impact for one of the 3 variables of interest. In that instance, 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 correcting for the stratification of the sample.

Katherine B Meaker, M.S.
Mathematical Statistician

Concur: Dr. Nevius 8-19-97

Dr. Kammerman 8/18/97

cc:
Archival NDA 20-527
HFD-580
HFD-580/TvanderVlugt, HJolson, LRarick
HFD-580/DMoore
HFD-715/ENevius, LKammerman, KMeaker, Chron

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-527/S-006

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEC 11 1997

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Division of Pharmaceutical Evaluation II

NDA 20-527
Supplement S-006

SUBMISSION DATES: January 9, 1997

PREMPRO™ Tablets
Conjugated Estrogens/Medroxyprogesterone Acetate
Wyeth-Ayerst Laboratories
Philadelphia, PA

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Supplement: New Dosing Regimen

SYNOPSIS:

On January 9, 1997, Wyeth-Ayerst submitted Supplement S-006 to NDA 20-527 for Prempro Tablets [conjugated estrogens (CE)/ medroxyprogesterone acetate (MPA)]. The purpose of this submission is to provide for a new continuous combined regimen of 0.625 mg CE/5 mg MPA for Prempro Tablets.

The clinical safety and efficacy information needed to support the proposed regimen for Prempro Tablets was included in the original NDA 20-303 which was approved on December 31, 1994. However, at that time, FDA did not approve the continuous combined 28-day regimen of 0.625 mg CE/5 mg MPA. The Agency's rationale was that the efficacy results, in terms of treating vasomotor symptoms and preventing endometrial hyperplasia, were indistinguishable for the 0.625 mg CE/2.5 mg MPA continuous combined regimen vs. the continuous combined 0.625 mg CE/5 mg MPA regimen.

In support of the continuous combined regimen of 0.625 mg CE/5 mg MPA for Prempro Tablets, this Supplement (S-006) to NDA 20-527 includes the following documents:

- "Recommendation of Expert Consultants on the Premarin 0.625 mg/MPA 5 mg 28-Day Continuous Combined Regimen"
- "Market research on the Use of 5 mg Progestin with 0.625 mg Estrogen as Continuous Combined HRT Regimen"
- "Proposed Draft Labeling for Prempro"

This supplement does not include any pharmacokinetic information. However, the clinical pharmacology and biopharmaceutic studies that were included in the original NDAs 20-303 and 20-527 (approved on November 17, 1995), are appropriate to support the new dosing regimen proposed in this Supplement to NDA 20-527 for Prempro Tablets. An overall summary of the clinical pharmacology

and biopharmaceutic studies previously submitted under NDAs 20-303 and 20-527 is presented in Attachment I.

LABELING

The sponsor's proposed labeling included in this Supplement is not acceptable. The **"CLINICAL PHARMACOLOGY"** and **"Pharmacokinetics"** sections of the proposed labeling need to be revised to incorporate the recommended changes described in Attachment II.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the information included in Supplement S-006 to NDA 20-20-527 dated January 9, 1997 for Prempro Tablets. Based on the review of the submitted information, OCPB/DPEII is of the opinion that the sponsor's proposed new dosing continuous combined 28-day regimen of 0.625 mg CE/5 mg MPA for Prempro Tablets is acceptable, provided the Clinical Pharmacology and Pharmacokinetic sections of the labeling are revised as appropriate to incorporate the recommended changes described in Attachment II.

Additionally, it is recommended that the sponsor revise the **"CLINICAL PHARMACOLOGY"** and **"Pharmacokinetics"** sections of PREMPHASE labeling to incorporate as appropriate the changes that were recommended for PREMPRO's labeling.

Lastly, the sponsor should be aware that the Agency has concerns regarding the term included in PREMPRO/PREMPHASE labelings. Currently, the Agency is evaluating information related to the term that was used to describe the formulation for conjugated estrogens. If the results of this evaluation indicate that the term is appropriate, then the Agency would ask for the revision of PREMARIN's labeling and incorporation (as appropriate) of the changes recommended for the **"CLINICAL PHARMACOLOGY"** and **"Pharmacokinetics"** sections of PREMPRO's labeling. However, if the results indicate that the use of this term is not appropriate, then the Agency would ask for the removal of the term from PREMPRO/PREMPHASE labelings.

12/11/97

Angelica Dorantes, Ph.D.
Pharmacokinetic Evaluation Branch II
Office of Clinical Pharmacology and Biopharmaceutics

RD Initialed by John Hunt. 12/10/97
FT Initialed by John Hunt. 12/11/97

cc: NDA 20-527/S-006 HFD-580 (van der Vlugt, Moore), HFD-870 (Chen, Dorantes), and CDR [B. Murphy for Drug]).

ATTACHMENT I

Includes;

NDA 20-527/S-006

Pharmacokinetic Information

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTIC STUDIES

The pharmacokinetic characteristics of the CE/MPA Tablets were evaluated in seven studies submitted under NDA 20-527. These studies are identified as follows: three pilot studies (713-B-107-US, 713-B-101-US and 713-B-109-US), two definitive bioequivalence studies (713-B-104-US and 713-B-111-US), and two food effect studies (713-B-112-US and 713-B-115-US). No metabolic, drug-drug interactions or special population (i.e., renal disease, hepatic disease, etc.) studies were submitted under NDA 20-527. However, the interaction between conjugated estrogens and medroxyprogesterone acetate was evaluated in Study 713-B-103-US included in NDA 20-303. An overall summary of the above clinical pharmacology and biopharmaceutic studies is presented next.

NDA No./ Study No.	Study Type	Drug/Dosage	No. Patients included in PK analysis
NDA 20-527 Pilot 713-X-107-US	Comparative Bioavailability Open-label, single dose, 5-treatment, 6-period, randomized crossover	Premarin (2x0.625) tablets + MPA (2x 2.5 mg encapsulated tablets) given concomitantly vs. one of the four CE/MPA 2x CE (0.625 mg)/MPA (2.5 mg) combination tablet formulations	12 women* years)
NDA 20-527 Pilot 713-X-101-US	Comparative Bioavailability Open-label, single dose, 2-treatment, 3-period , randomized crossover	Premarin (2x0.625) tablets + MPA (2x 5.0 mg encapsulated tablets) given concomitantly vs. 2x CE/MPA (0.625 mg/5.0 mg) combination tablets	51 women* years)
NDA 20-527 Pilot 713-B-109-US	Comparative Bioavailability Open-label, single dose, 5-treatment, 7-period, randomized crossover	Premarin (2x0.625) tablets + MPA (2x 5.0 mg encapsulated tablets) given concomitantly vs. one of the four CE/MPA combination tablet formulations (one CE/MPA and three CE placebo/MPA + Premarin)	20 women* years)
NDA 20-527 Pivotal 713-X-104-US	Bioequivalence Open-label, single dose, 2-treatment, 3-period , 4-sequence, randomized crossover	Premarin (2x0.625) tablets + MPA (2x 2.5 mg encapsulated tablets) given concomitantly vs. 2x CE (0.625 mg)/MPA (2.5 mg) combination tablets	50 women* years)
NDA 20-527 Pivotal 713-X-111-US	Bioequivalence Open-label, single dose, 2-treatment, 3-period , 4-sequence, randomized crossover	Premarin (2x0.625) tablets + MPA (2x 5.0 mg encapsulated tablets) given concomitantly vs. 2x CE (0.625 mg)/MPA (5.0 mg) combination tablets	51 women* years)
NDA 20-527 Pivotal 713-B-112-US	Food Effect Open-label, single dose, 2-treatment, 2-period , randomized crossover	2x CE (0.625 mg)/MPA (2.5.0 mg) combination tablets given in the fasting state or immediately after ingestion of a standard high-fat meal	20 women* years)
NDA 20-527 Pivotal 713-B-115-US	Food Effect Open-label, single dose, 2-treatment, 2-period , randomized crossover	2x CE (0.625 mg)/MPA (5.0 mg) combination tablets given in the fasting state or immediately after ingestion of a standard high-fat meal	20 women* years)
NDA 20-303 Pivotal 713-B-103-US	Drug Interaction Open-label, single dose, randomized 3-period crossover	Premarin (2x0.625 mg) tablets vs. MPA (2x5.0 mg) encapsulated intact tablets vs. Premarin (2x0.625 mg) tablets plus MPA (2x5.0 mg) encapsulated intact tablets given concomitantly	52 women*

*Healthy postmenopausal or surgically sterilized women

Pilot: Three pilot relative bioavailability studies were performed during the development of the combination tablets. Study **713-B-107-US** evaluated preliminary formulations of 0.625 mg/2.5 mg CE/MPA tablets, and studies **713-B-101-US** and **713-B-109-US** evaluated preliminary formulations of 0.625 mg/5.0 mg CE/MPA tablets. Based on the results of these pilot studies the to be-marketed formulations for both strengths were selected and further developed.

Bioequivalence: Study **713-B-104-US** evaluated the bioequivalence of 2x0.625 mg/2.5 mg CE/MPA combination tablets (to-be-marketed) vs. 2x0.625 mg Premarin tablets and 2x2.5 mg encapsulated MPA tablets, and study **713-B-111-US** evaluated the bioequivalence of 2x0.625 mg/5.0 mg CE/MPA combination tablets (to-be-marketed) vs. 2x 0.625 mg Premarin tablets and 2x 5.0 mg encapsulated MPA tablets. The results of these studies indicate that the 90% confidence limits for log-transformed Cmax and AUC of estrogens and MPA are within the 80-125% bioequivalence criteria. Therefore, the CE/MPA 0.625/2.5 mg and CE/MPA 0.625/5.0 mg tablets were bioequivalent to the separate Premarin tablets and encapsulated MPA tablets administered concomitantly.

Food-Effect: Study **713-B-112-US** and study **713-B-115-US** studied the effect of food on the bioavailability of CE and MPA with the to-be-marketed 0.625 mg/2.5 mg CE/MPA and 0.625 mg/5.0 mg CE/MPA tablets, respectively. The overall results indicate that food did not affect the extent of absorption/formation of the various estrogens, but food reduced the Cmax of total estrone by 34% and increased MPA Cmax and AUC0-∞ (For studies 713-B-112-US and 713-B-115-US food increased MPA Cmax by 115 and 84% and AUC0-∞ by 28% and 16%, respectively). It should be noted that similar results were observed for the food-effect study 713-B-114-US submitted under the already approved NDA 20-303 for CE/MPA separated tablets. In this study, food reduced total estrone Cmax by 18%, increased total equilin by 38% and increased MPA Cmax and AUC0-∞ by 89% and 28%, respectively.

Drug-Interaction: Study **713-B-103-US** was designed to investigate potential pharmacokinetic interaction between Premarin and medroxyprogesterone acetate (MPA) when given as a combined regimen. This was a single dose, randomized, three period crossover study in which 52 subjects received single oral doses of Premarin (2 x 0.625 mg) administered alone, MPA (2 x 5 mg encapsulated intact tablets) administered alone, and Premarin tablets and MPA encapsulated tablets administered concomitantly. The results of this study indicate that single dose coadministration of 2x0.625 mg Premarin tablets with 10 mg (2x5 mg encapsulated intact tablets) MPA does not affect the pharmacokinetics of estrone, equilin, total estrone, total equilin, or MPA. In conclusion, the results indicate that there is no pharmacokinetic interaction between Premarin and MPA.