

FEB 25 1997

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 25, 1997

FROM: Angelica Dorantes, Ph.D., Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

TO: Division of Reproductive and Urologic drug Products

ISSUE: Filing of NDA 20-527 for PREMPRO (Conjugated Estrogens/MPA) Tablets

SYNOPSIS

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

The pharmacokinetic and clinical information to support the proposed regimen for Prempro Tablets was included in original NDA 20-303 which was approved on December 31, 1994. However, at that time, FDA did not approve

The Agency's rationale was that the efficacy results, in terms of treating vasomotor symptoms and preventing endometrial hyperplasia, were indistinguishable for the

In support of the continuous combined regimen of 0.625 mg CE/5 mg MPA for Prempro Tablets, this application 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"

The sponsor did not include any pharmacokinetic information in this supplement. However, the pharmacokinetic information included in the original NDA 20-303 is appropriate to support this application to NDA 20-527 for Prempro Tablets.

A summary of the studies included in the original NDA 20-303 is presented in Table 1.

TABLE 1

Protocol Number	Study Type	Drug/Dosage	No. of Patients
713-X-110-US	Comparative Bioavailability Open-label, single dose, 2-treatment, 3-period, 4-sequence, randomized crossover	Premarin (2x0.625) trade tablets (contains talc triturate) vs. Premarin(2x0.625) talc triturate-free tablets	52
713-B-103-US	Metabolic 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
713-B-114-US	Food Effect Open-label, single dose given concomitantly with and without food 2-treatment, 2-period, randomized crossover	Premarin(2x0.625 mg) tablets and MPA (2.5 mg) tablets	20

Study 713-X-110-US, titled "***A Comparative Bioavailability Study of Currently Marketed Premarin® Tablets (0.625 mg) and a Research Formulation of Premarin Tablets (0.625 mg)***", was designed to evaluate and compare the relative bioavailability of Premarin research tablet and the currently marketed Premarin tablet. This was an open-label, single dose, randomized, two-treatment, three period crossover study, in which fifty-three women were enrolled and 52 completed the study. Each subject received single oral doses of 2 x 0.625 mg Premarin as one of the two formulations on three separate occasions. Blood samples were collected at specific times for 48 hours after administration. Plasma concentrations of estrone, equilin, total estrone, total equilin, 17b-estradiol, and 17b-dihydroequilin were analyzed by

methods were used to analyze the data for each component. The statistical results indicate that the 90% confidence limits for the pharmacokinetic parameters of the evaluated estrogens were within the % bioequivalence criteria.

Study 713-B-103-US, titled "***A Pharmacokinetic of Premarin® and Medroxyprogesterone Acetate Following Concomitant Administration in Postmenopausal Women***", 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 54 women were enrolled and 52 completed the

study. Each subject 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. Blood samples were collected at specific times for 48 hours after administration of Premarin and for 144 hours after administration of MPA. Plasma concentrations of estrone, equilin, total estrone, total equilin, 17 β -estradiol, and 17 β -dihydroequilin were analyzed by

methods were used to analyze the data for each component. Bioequivalence tests on comparative bioavailability parameters were based on least-square mean ratios and 90% C.I. using log-transformed data. 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.

Study 713-B-114-US, titled "***A Study of the Effects of Food on the Pharmacokinetic of Premarin® (0.625 mg) Tablets and Medroxyprogesterone Acetate (MPA, 2.5 mg) Tablets Administered Concomitantly in Healthy Postmenopausal Female Subjects***", was designed to evaluate the effect of food on the relative bioavailability of 0.625 mg Premarin tablets and 2.5 mg medroxyprogesterone acetate tablets. This was an open-label, single dose, randomized, two-treatment, two-period crossover study conducted in 20 postmenopausal women. Each subject received single oral doses of Premarin (2 x 0.625 mg) and MPA (2 x 2.5 mg) either in a fasting state or immediately following a standardized high-fat breakfast on two separate occasions. Blood samples were collected at specific times for 144 hours after administration. Plasma concentrations of several estrogens were analyzed by

methods were used to analyze the data for each component. Statistical comparisons were made using an analysis of variance for a three period crossover design. Bioequivalence tests on comparative bioavailability parameters were based on least-square mean ratios and 90% C.L. using log-transformed data. The overall results indicate that there is a food effect. Administration of Premarin with food slowed the absorption of the conjugated estrogens; C_{max} was reduced by 25% to 30%, but AUC was not affected. With respect to the bioavailability of MPA, food significantly increased medroxyprogesterone C_{max} and AUC_{0-∞} by 89% and 28%, respectively.

Also, it should be noted that additional pharmacokinetic information for Prempro Tablets was included in NDA 20-527 for CE (0.625 mg) and MPA (2.5 mg) and a CE (0.625 mg) and MPA (5.0 mg) combination tablets. This NDA was filed on November 18, 1994 and approved on November 1995.

In NDA 20-527, the pharmacokinetic characteristics of the CE/MPA combination tablets were studied in seven studies. These studies are identified as follows: two definitive bioequivalence studies (713-B-104-US and 713-B-111-US), three pilot studies (713-B-107-US, 713-B-101-US and 713-B-109-US), and two food effect studies (713-B-112-US and 713-B-115-US). The 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 combination tablets, and studies **713-B-101-US** and **713-B-109-US** evaluated preliminary formulations of 0.625 mg/5.0 mg CE/MPA combination tablets.

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 statistical results indicate that the 90% confidence limits for the pharmacokinetic parameters of the evaluated estrogens were within the 80-125% bioequivalence criteria.

Food-Effect: Study **713-B-112-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 combination tablet and study **713-B-115-US** with the to-be-marketed 0.625 mg/5.0 mg CE/MPA combination tablet. The overall results indicate that there is a food effect.

RECOMMENDATION:

From the clinical pharmacology and biopharmaceutics viewpoint, the supplemental application to NDA 20-527 submitted on January 9, 1997 for Prempro Tablets is fileable.

CC: NDA 20-527, HFD-580 (van der Vlugt, Moore), HFD 870 (Chen; PKLN 13B-17, Dorantes), HFD-850 (Millison; WOC2 3010 for Drug file)

NDA: 20-527/S-006

45 Day Filing Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) Is the clinical section of the NDA clearly organized?	✓		In original submission for NDA 20-303
2) Is the clinical section of the NDA adequately indexed and paginated?	✓		"
3) Is the clinical section of the NDA legible?	✓		"
4) Is there an adequate rationale for selection of dose and dosing schedule?	✓		"
5) Are the requisite number of adequate and well controlled studies submitted in the application?	✓		"
6) Are the pivotal efficacy studies of appropriate design and duration to assess approvability of this product for its proposed indication?		✓	NDA 20-303 was not evaluable for the indication of osteoporosis prevention and did not contain evidence of efficacy for treatment of osteoporosis.
7) Are electronic data sets (with adequate documentation for their use) provided for pivotal efficacy studies?		✓	Not applicable for 1992
8) Has the applicant submitted line listings in a format to allow review of individual patient data?	✓		In original submission for NDA 20-303
9) Has the applicant submitted a rationale for assuming the applicability of foreign trial results to the U.S. population?	✓		Clinical studies conducted in Belgium, Finland, Germany, Italy, Netherlands and Switzerland
10) Has the applicant submitted all required case report forms (i.e., deaths, drop-outs due to ADEs and any other CRFs previously requested by the Division)?	✓		

ITEM	YES	NO	COMMENT
11) If appropriate, have stratified analyses of primary safety and efficacy parameters been conducted for age, gender and race?			<i>Not applicable</i>
12) Has the applicant presented the safety data in a manner previously agreed to by the Division?	✓		<i>In original submission for NDA 20-303</i>
13) If approved in other countries, have a summary and assessment of foreign post-marketing experience been provided?			<i>Not applicable</i>
14) Has draft labeling been submitted?	✓		
15) Have all special studies/data requested by the Division during pre-submission discussions with the sponsor been submitted?	✓		
16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	✓		
17) Reasons for refusal to file:			

J.H. van der Vliet MD, 3/4/97
 Reviewing Medical Officer / Date

\45dfile

NDA 20-527/SE2-006

Wyeth-Ayerst Laboratories
Attention: Ms. Joan E. Barton
Associate Director
Women's Health Care Products
U.S. Drug Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Barton:

Please refer to your pending January 8, 1997, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PREMPRO™ (conjugated estrogens/medroxyprogesterone acetate) Tablets.

We have reviewed the labeling in your submission and have updated the Clinical Pharmacology and Biopharmaceutics sections. In addition, we have made revisions in several other sections of the labeling. We have enclosed a draft copy of these revisions incorporated directly into the physician and patient package inserts. The additions that you suggested in your supplemental application are noted in redline. Your suggested deletions have been retained as ~~strikeouts~~. FDA additions have been noted in double underline, FDA deletions have been noted as ~~double underlined strikeouts~~. FDA deletions to your proposed changes are noted as ~~redline strikeouts~~. Additional comments requiring response are in **14 pt bold face type**. A clean copy of the revised labeling and an electronic copy in WordPerfect have been included for your convenience.

Additionally, the "CLINICAL PHARMACOLOGY" and "Pharmacokinetics" sections of PREMPHASE labeling should be revised to incorporate the appropriate changes that were recommended for PREMPRO's labeling.

Lastly, the Agency has concerns regarding the _____ term included in the 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, the PREMARIN labeling should be revised to incorporate the appropriate changes made to the "CLINICAL PHARMACOLOGY" and "Pharmacokinetics" sections of PREMPRO's labeling. However, if the results indicate that the use of this term is not appropriate, the _____ term should be removed from the PREMPRO/PREMPHASE labelings.

We would appreciate your prompt written response so we can continue our evaluation of your supplemental application.

NDA 20-527/SE2-006

Page 2

If you have any questions, please contact Diane Moore, Project Manager, at (301) 827-4260.

Sincerely,

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

enclosures:

draft copy of revisions to the PREMPRO label

clean copy of the revised PREMPRO label

NDA 20-527/SE2-006

Page 3

cc:

Original NDA 20-527

HFD-580/Div. Files

HFD-580/CSO/D.Moore

HFD-580/LRarick/HJolson/Tvan der Vlugt/MRhee/RSeEVERS/KRaheja/AJordan/LKammerman

HFD-580/ADorantes/GBarnette

HFD-820/ONDC Division Director (only for CMC related issues)

HFD-40/DDMAC/LStockbridge

Drafted by: dm/December 2, 1997/n20527

Concurrences:

LPauls 12.03.97/Tvan der Vlugt, RSeEVERS, MRhee, KRaheja 12.04.97

AJordan, LStockbridge, KMeaker 12.05.97/LKammerman 12.08.97

HJolson/ADorantes 12.11.97/LRarick 12.17.97

INFORMATION REQUEST (IR)



NDA 20-527/S-006

JAN 17 1997

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

Attention: Joan E. Arton, Associate Director
Marketed Products
U.S. Drug Regulatory Affairs

Dear Ms. Barton:

We acknowledge receipt of your supplemental application for the following:

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

NDA Number: 20-527

Supplement Number: S-006

Date of Supplement: January 8, 1997

Date of Receipt: January 9, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on March 10, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-527/S-006

Page 2

cc:

Original NDA 20-527/S-006

HFD-580/Div. Files

HFD-580/CSO/Moore

SUPPLEMENT ACKNOWLEDGEMENT

MEETING MINUTES

Date: September 15, 1997 Time: 10:00 - 10:50 AM Location: Parklawn; Rm 17B-43

NDA: 20-527/S-006 Drug Name: PREMPRO™ (conjugated estrogens/medroxyprogesterone acetate) Tablets

Type of Meeting: Labeling

Meeting Chair: Dr. Heidi Jolson

Meeting Recorder: Mrs. Diane Moore

FDA Attendees:

- Heidi Jolson, M.D., M.P.H. - Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
- Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
- Diane Moore - Consumer Safety Officer, DRUDP (HFD-580)
- Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
- Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
- Lisa Stockbridge, Ph.D. - Regulatory Review Officer, DDMAC (HFD-40)

Meeting Objectives:

To discuss labeling changes for the efficacy supplement.

Discussion Points:

- ◆ Boxed warning
 - ◆ the updating of the boxed warnings is in progress
- ◆ Clinical
 - ◆ the information describing the clinical trial results is dispersed throughout the **CLINICAL PHARMACOLOGY** section; it should be pooled and placed at the end of the **CLINICAL PHARMACOLOGY** section under a Clinical Studies subsection
 - ◆ the study numbers in the tables and text appear to be placed appropriately
 - ◆ on page 4 of the labeling, the new paragraph requested by the sponsor that begins, "Of the 59 patients . . ." should be shortened to one sentence; it is promotional and does not refer to the prescribed indication of endometrial hyperplasia
 - ◆ the wording the sponsor has requested to be deleted that begins, "Sixteen to twenty percent . . ." should be retained instead of the replacement paragraphs the sponsor has suggested
 - ◆ the new figures suggested by the sponsor in the **CLINICAL PHARMACOLOGY** section are inappropriate

- ◆ the sponsor references a lower dropout rate and difference in bleeding from the two doses; a previous review of the data concluded that the difference was not clinically significant
- ◆ the labeling does not encourage the use of the lower 2.5 mg dose prior to using the higher 5.0 mg dose
- ◆ **Biometrics**
 - ◆ **INFORMATION REGARDING LIPID EFFECTS**
 - ◆ although the numbers are acceptable in the chart entitled, "MEAN PERCENT CHANGE FROM BASELINE LIPID PROFILE VALUES AFTER ONE YEAR OF TREATMENT" the lipid results are suspicious when compared with previous studies; the chart shows lipid is lowered with Premarin added to progesterone; the total cholesterol LDL goes down when compared to Premarin
 - ◆ the "n" numbers should be inserted under the headings Premarin, PREMPRO 0.625 mg/2.5 mg and PREMPRO 0.625 mg/5 mg. They are as follows:
 - Premarin, n=86
 - PREMPRO 0.625 mg/2.5 mg, n =90
 - PREMPRO 0.625 mg/5 mg, n=84
 - ◆ the market survey polled physicians who prescribed the HRT drug regimen; only 2% of physicians selected in the sample were contacted (405 physicians); the completion rate on the survey was low; the market survey data should not be used in advertising or labeling

Decisions:

- ◆ the **CLINICAL PHARMACOLOGY** section should be reformatted including a one-line introduction to the section
- ◆ the **CLINICAL PHARMACOLOGY** issues will be revisited at the next labeling meeting
- ◆ **ADVERSE REACTIONS** section
 - ◆ a 3-column comparative table with most of the common adverse reactions will be proposed by the statistician using intent-to-treat population irregardless of causality to replace the list in the adverse reactions section
 - ◆ the percent cutoff (usually 5%) can be chosen from the endometrial hyperplasia study
- ◆ **DOSAGE AND ADMINISTRATION** section
 - ◆ item 1. The paragraph that begins, "For treatment of moderate . . ." will be rewritten by the Medical Officer
- ◆ the sponsor will need to submit a labeling supplement (SLR) to incorporate this label with the combined label

Action Items:

- | Item: | Responsible Person: | Due Date: |
|--|----------------------------|------------------|
| ◆ revisit the status of the boxed warnings updates | Dr. van der Vlugt | two weeks |
| ◆ draft a sentence to replace bleeding patterns of two doses | Dr. van der Vlugt | two weeks |

- ◆ redraft the paragraph comparing the bleeding data from the two doses

Dr. van der Vlugt and
Ms. Meaker

two weeks

Signature, minutes preparer

10/20/97

Concurrence, Chair

10/20/97

drafted: dm/09.16.97/n20527s6.915

NDA Arch:

HFD-580

HFD-580/LRarick/HJolson/Tvander Vlugt/KMeaker/LKammerman/Jordan/KRaheja/ADorantes

HFD-580/JMercier

Concurrences:

LPauls 09.19.97/KMeaker 09.29.97/LStockbridge 10.01.97/Tvan der Vlugt, HJolson 10.17.97
LKammerman 10.17.97

Moore

Meeting MINUTES

Date: June 24, 1997 Time: 11:00 - 11:30 AM Location: Parklawn; Rm 17B-43

NDA: 20-527/S-006 Drug Name: PREMPRO™ (conjugated estrogens/medroxyprogesterone acetate) Tablets

External Participant: Wyeth-Ayerst Research Laboratories

Type of Meeting: 5 Month Status

Meeting Chair: Dr. van der Vlugt

Meeting Recorder: Mrs. Diane Moore

FDA Attendees:

- Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
- Diane Moore - Consumer Safety Officer, DRUDP (HFD-580)
- Angelica Dorantes, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
- Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
- Tatiana Pavlova M.D., Ph.D. - Clinical Pharmacology Fellow @ DRUDP (HFD-580)

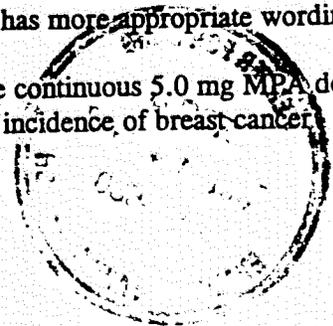
External Constituents: None

Meeting Objectives:

Meeting to discuss status of the reviews for this Efficacy Supplement (NDA 20-527/S-006).

Discussion Points:

- ◆ Medical
 - ◆ review in progress; supplement appears to be approvable
 - ◆ the Dosage and Administration section of the label should have stronger wording to indicate that the 5.0 mg dose of MPA should never be the primary regimen of choice for HRT
 - ◆ the evaluation of irregular vaginal bleeding should be discussed in the label
 - ◆ the original Prempro™ label for 2.5 mg dose of MPH has more appropriate wording than this proposed label
 - ◆ the data from breast cancer studies are conflicting; the continuous 5.0 mg MPA dose remains under review and appears to not increase the incidence of breast cancer
- ◆ Chemistry - review complete and approvable
 - ◆ EER status pending



- ◆ Biopharmaceutics: approvable with labeling comments; changes in the pharmacokinetics section and the order of the labeling subheadings will need to be discussed at the labeling meeting
- ◆ Biometrics: additional information regarding the market research surveys has been provided by the sponsor; the review is targeted for completion at the end of July 1997
- ◆ the labeling meeting is scheduled for July 28, 1997, at 10:00 AM

Signature, minutes preparer

7/7/97

Concurrence, Chair

7/19/97

drafted: dm/n20527s6.624/06.24.97

cc:

NDA Arch:

HFD-580

HFD-580/LRarick/HJolson/Tvander Vlugt/KMeaker/LKammerman/Jordan/KRaheja/ADorantes

HFD-580/JMercier

HFD-715/ENevius

HFD-580/TPavlova

Concurrences:

TRumble 06.24.97/Tvan der Vlugt, ADorantes, KMeaker 06.25.97/TPavlova 07.01.97

MINUTES of TELECON

Date: June 17, 1997 **Time:** 10:30 - 10:40 AM **Location:** Parklawn; Rm 17B-43

NDA: 20-527/S-006 **Drug Name:** PREMPRO™ (conjugated estrogens/medroxyprogesterone acetate) Tablets

External Participant: Wyeth-Ayerst Research Laboratories

Type of Meeting: Statistical Guidance

Meeting Chair: Ms. Kate Meaker

External Participant Lead: Ms. Joan Barton

Meeting Recorder: Mrs. Diane Moore

FDA Attendees:

Diane Moore - Consumer Safety Officer, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

External Constituents:

Joan Barton - Associate Director, Women's Healthcare, Regulatory Affairs

Robert Quinty - Regulatory Coordinator

Jeff Buchalter - Marketing Planning

Nick Farkalas - Market Research

Mike Temple - Statistician, Market Research

Gail Ludmurer - Market Planning

Dave LaSente, M.D. - Medical Affairs

Meeting Objectives:

To discuss statistical questions regarding the Market Survey submitted in Supplement 006 of NDA 20-527.

Discussion Points: (See attached)

- ◆ Question 1: the information in the June 2, 1997, submission from Wyeth-Ayerst was compared to the information submitted in the original submission for Supplement 006; there were discrepancies found between the two submissions
 - ◆ in the table on the first page of the June 2, submission, the entire population of physicians polled are Obstetricians and Gynecologists (OB/GYNs) or primary care providers in the U.S.
 - ◆ the Xponent data base in the original submission was comprised of the whole population of OB/GYN and PCP physicians

Meeting Minutes - June 17, 1997

- ◆ Question 2: the Xponent Prescription Tracking Database represents physicians and physician prescribing behavior; the database is developed independently of Wyeth-Ayerst
- ◆ Question 3a: the ordering/definition of the quintiles occurred before the 20,000-name sample was selected
 - ◆ the entire database was used to select a systematic sample
 - ◆ the file was ordered by quintiles and sampled from the entire file
 - ◆ in the June 2 submission, the 20,000 names were selected from the entire list in the Xponent database
 - ◆ 10,000 names were selected from each specialty
- ◆ Question 3b: quotas were only designated for specialty; quintiles were used to obtain representation of each size group of doctors within each specialty; the sample was ordered by quintiles and selective sampling was used to get the 20% per quintile
- ◆ Question 4: no, the values used to determine quintiles in the June 2 submission were based on the number of prescriptions written rather than the number of physicians; the quintile for the study represents the number of physicians; the difference in the reports occurred because there was a transition phase between sample selection for this study and May 1997 when population figures were requested; usually quintiles are made by the number of prescriptions written; the figures in the June 2 submission were based on 1347 physicians who wrote the top 20% of OB/GYN prescriptions; when sampling, 2005 OB/GYN was based on the doctors who wrote the most prescriptions

Action Items: None

Signature, minutes preparer

1/8/98

Concurrence, Chair

1/8/98

drafted: dm/n20527s6.617/06.19.97

cc:

NDA Arch:

HFD-580

HFD-580/LRarick/HJolson/KMeaker/LKammerman

HFD-580/JMercier

HFD-715/ENevius

Concurrence:

LPauls 01.06.98/KMeaker 01.07.98

NDA 20-527 / S006

Prempro
Wyeth-Ayerst
Supplemental Application - Market Research Study

Questions for Telecon on 6/17/97

1. The sample was randomly selected from the Xponent database. Is there any way to confirm that the Xponent database is representative of the whole population of OB/GYN and PCP physicians ?

2. Is the Xponent database independent of Wyeth-Ayerst?
[In supplement, pg. 43, it says the list was provided by W-A]

3. In the supplement package (pg 43), the sampling method is described as follows:
start with list of physicians
split by specialty
within each specialty:
 order physicians,
 define quintiles,
 assign codes 1 thru 5 to physicians
re-combine full list
randomly select 20% per quintile, regardless of specialty
 - a. Regarding the 20K sample reported in the 6/2 fax....did the ordering/definition of the quintiles occur before or after the 20K was selected?
If before, from what larger list?
If after, how many were selected and what was the distn. by specialty?

 - b. Was the selection made within specialty (10K each) or by quintile regardless of specialty [as in suppl. description]?

NDA 20-527 / S006

Prempro
Wyeth-Ayerst
Supplemental Application - Market Research Study

Questions for Telecon on 6/17/97

4. In the population figures (first table) reported in the 6/2 fax, were the cutoff values used to define the quintiles the same as those used for the sample of 10K per specialty?

If no, explain sampling quotas actually used because it differs from info in suppl. description.
If yes, how can there be 1347 OB/GYN Quin=5 in the population and 2005 in the sample?

NDA 20-527 / S006

Prempro
Wyeth-Ayerst
Supplemental Application - Market Research Study

Questions for Telecon on 6/17/97

1. The sample was randomly selected from the Xponent database. Is there any way to confirm that the Xponent database is representative of the whole population of OB/GYN and PCP physicians ?

2. Is the Xponent database independent of Wyeth-Ayerst?
[In supplement, pg. 43, it says the list was provided by W-A]

3. In the supplement package (pg 43), the sampling method is described as follows:
start with list of physicians
split by specialty
within each specialty:
 order physicians,
 define quintiles,
 assign codes 1 thru 5 to physicians
re-combine full list
randomly select 20% per quintile, regardless of specialty
 - a. Regarding the 20K sample reported in the 6/2 fax....did the ordering/definition of the quintiles occur before or after the 20K was selected?
If before, from what larger list?
If after, how many were selected and what was the distn. by specialty?

 - b. Was the selection made within specialty (10K each) or by quintile regardless of specialty [as in suppl. description]?