CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-527/S-006

ADMINISTRATIVE DOCUMENTS

Group Leader Memorandum

NDA:	**20-527/SE-006**
Drug and indications:	**Prempro™ [conjugated estrogens (CEE)/medroxyprogesterone acetate (MPA)] tablets for use in women with an intact uterus for the treatment of moderate to severe vasomotor symptoms; treatment of vulvar and vaginal atrophy; and prevention of osteoporosis**
Dose:	**0.625/5 mg orally once daily**
Applicant:	**Wyeth Ayerst**
Submission dated:	**January 8, 1997**
Date of MO review:	**January 6, 1998**
Date of Memorandum:	**January 6, 1998**

In this application, the sponsor requests approval for an additional strength of the marketed product Prempro (originally approved under NDA 20,303 in December 1994). The new dosage strength provides for a higher dose of MPA (5 mg) in combination with 0.625 mg CEE in women for whom bleeding or spotting is problematic on the 0.625/2.5 mg dose. The previously submitted and reviewed clinical trial #713B-300 provides evidence of the safety and efficacy of both Prempro regimens in preventing endometrial hyperplasia.

In the initial application, the 0.625 mg/5 mg dosage was not approved because the clinical trial demonstrated that it was equally effective to the 0.625 mg/2.5 mg dosage in preventing endometrial hyperplasia but was judged to offer no clinical advantage in terms of less bleeding (that resulted in treatment discontinuation). This supplemental applications provides further discussion of this issue and provides marketing information that suggests that 5 mg of MPA is prescribed frequently by physicians to reduce bleeding and spotting with 0.625 mg CEE.

I concur with the recommendation of the primary medical officer that this supplemental application be approved. Although only a small difference in amenorrhea rates between Prempro dosage groups was demonstrated, this small difference may be clinically important for those women requiring HRT and in whom bleeding is problematic. Further, extensive post-marketing experience with these products suggests that there are no safety issues with the 5 mg dose of MPA that would offset the potential benefit of better compliance with HRT.

This new tablet strength should be approved for use in all three of Prempro's current indications (including osteoporosis) between a previously reviewed drug interaction study demonstrated that

5 mg of MPA does not have a clinically important effect on the pharmacokinetics of Premarin.

There are no outstanding regulatory issues. The most recent draft Prempro labeling is generally acceptable, with the changes agreed-upon in a teleconference on January 6, 1998. The sponsor was encouraged to submit revised combination Prempro/Premphase labeling post-approval.

Heidi M. Jolson, M.D., M.P.H.
Deputy Division Director, HFD-580

cc:
NDA20-527
HFD-580/LRarick/T van der Vlugt/HJolson

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Prempro™ (Conjugated estrogens/medroxyprogesterone acetate) Tablets
Wyeth-Ayerst Research

Division Director's Memo

The application will be signed off at the Division level. No memo is necessary.

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Patent Information

No information provided.

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Exclusivity Summary

Exclusivity was not requested because this application does not qualify for exclusivity.

JAN 2 1998

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-527/SE6 Trade (generic) names: Prempro™ (conjugated estrogens/medroxyprogesterone acetate) Tablets

Check any of the following that apply and explain, as necessary, on the next page:

___ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

___ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

___ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

___ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

___ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

___ a. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.
___ (2) Protocols have been submitted and approved.
___ (3) Protocols have been submitted and are under review.
___ (4) If no protocol has been submitted, on the next page explain the status of discussions.

___ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

_X_ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

_____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

_____ 1/2/97

Signature of Preparer Date

cc: Orig NDA
HFD-580/Div File
NDA Action Package

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Debarment Certification

This efficacy supplement is based on literature references and a market research study. No debarrment statement is necessary.

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DSI Audit of Clinical Studies

No clinical studies were submitted under this application. Therefore no audit was required.

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Safety Update Review

This application was from a market research study, not clinical studies. No safety update is required.

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Federal Register Notices

This application was not the subject of any Federal Register Notices.

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EER

There were no manufacturing changes - no EER is required.

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Microbiology Review

No microbiology review is required for a market research survey.

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Advertising Material

No advertising material has been submitted.

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Efficacy Summary (ISS)

The efficacy summary is based on the information submitted to NDA 20-303 and a market survey, no new clinical studies were submitted. No safety summary is required.

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Safety Summary (ISS)

The safety summary is based on the information submitted to NDA 20-303 and a market survey, no new clinical studies were submitted. No safety summary is required.

NDA 20-527
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Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

MEETING MINUTES

Date: November 13, 1997 **Time:** 1:30 - 2:15 PM **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 - Project Manager, DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Angelica Dorantes, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Meeting Objectives:

To discuss changes in the Clinical and Biopharmaceutics sections of the labeling for the efficacy supplement.

Discussion Points:

- a description of the combined tablet is no longer appropriate because the drug is combined in a single tablet

Decisions:

- the changes in the labeling in the attached marked up label will be relayed to the sponsor; an additional copy of the label with the changes incorporated will also be sent for further clarification (see attached draft labeling)
- a new introduction paragraph to the **Clinical studies** subsection of the **Clinical Pharmacology** section will be drafted by the medical officer
- the **Pharmacokinetics** subsection of the **Clinical Pharmacology** section will be revised by the OCPB reviewer
- the two paragraphs that describe the pharmacologic effects and the androgenic and anabolic effects of MPA in the **Pharmacodynamic** section should be rewritten
- further changes to be made by the sponsor include the following items:
  - tables should be shown instead of descriptions for the Amenorrhea and Lipids subsections
  - the Food Effect description should be replaced by a Food Effects Table

- a table of the adverse events regardless of causality that occurred in ≥5% by treatment group should be proposed to replace the listing of adverse events

Action Items:

	Item:	Responsible Person:	Due Date:
♦	circulate corrections from meeting for comment	Mrs. Moore	one week

Signature, minutes preparer 12/1/97

Concurrence, Chair 12/2/97

Post Meeting Addendum: further discussions between the Medical Officer and Statistician suggested the addition of the total patient numbers of 340 for PREMPRO 0.625/2.5mg MPA; 338 for PREMPRO 0.625mg/5.0 mg MPA; and 347 for Premarin 0.625 for the total numbers of patients in the Table entitled, "Incidence of Endometrial Hyperplasia After One Year of Treatment." Asterisks should be added to the PREMPRO 0.625 mg/5 mg MPA column at the 0.00 numbers (compared to Premarin alone) to match the footnote to the table.

drafted: dm/11.19.97/n20527lb.113

NDA Arch:
HFD-580
HFD-580/LRarick/HJolson/Tvander Vlugt/KMeaker/LKammerman/Jordan/KRaheja/ADorantes
HFD-580/JMercier

Concurrences:
LPauls 11.20.97/KMeaker, HJolson 11.21.97/ADorantes 11.26.97/Tvan der Vlugt 12.01.97

MEMORANDUM

4/7/97

From: Robert H. Seevers, Reviewing Chemist

To: Division file on NDA 20-527

4/7/97

Through: Moo-Jhong Rhee, Chemistry Team Leader

Re: NDA 20-527 Supplement SE2-006

Date: April 7, 1997

The submission is an efficacy supplement for an additional strength, 0.625 mg Conjugated Estrogens/5 mg Medroxyprogesterone acetate, to the currently approved strength, 0.625 mg Conjugated Estrogens/2.5 mg Medroxyprogesterone acetate. This strength was submitted in the initial NDA, but only the lower strength of medroxyprogesterone acetate was approved. The chemistry of the higher strength combined tablet was reviewed by Steven Moore on 11/8/95 and 11/17/95 and found to be satisfactory. Supplement SE2 -006 may approved from a chemistry standpoint.