CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 4-782/S-093

MEDICAL REVIEW(S)

MEDICAL OFFICER'S CONSULTATION REPORT

NDA NO. 004-782
DRUG: PREMARIN®
GENERIC NAME: Conjugated Estrogens
MANUFACTURER: Wyeth-Ayerst
INDICATION: Post-Menopausal Osteoporosis
CONSULTATION REQUESTED BY:
Diane Moore
HFD-580
Division of Reproductive and Urologic Drug Products

DATE OF REQUEST: November 21, 1997
DESIRED COMPLETION: December 31, 1997
DATE REC'D., M.O.: December 10, 1997
DATE COMPLETED: December 12, 1997

THROUGH:
Solomon Sobel, M.D., Director Division of Metabolic and Endocrine Drug Products, HFD-510
Gloria Troendle, M.D., Deputy Director; Team Leader, DMEDP; HFD-510

Sobel 12-15-97

Material Examined: Supplement Amendment SE2-093; Osteoporosis Indication

SUMMARY: At a meeting between Wyeth-Ayerst and DMEDP on October 23, 1997, it was agreed that the osteoporosis data from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial may be incorporated into the Clinical Pharmacology - Clinical Studies subsection of the Premarin labeling. This supplement contains draft physician and patient labeling for this purpose. The data upon which these changes are based were reported in : The Writing Group for the PEPI Trial. Effects of Hormone Therapy on Bone Mineral Density. J. Am. Med. Assocn. Nov. 6, 1996, **276**, No. 17: 1389-1396.

MEDICAL OFFICER'S COMMENTS AND RECOMMENDATIONS

1. A sentence has been changed in the second paragraph of the Section on **Indications and Usage**, under **Prevention of Osteoporosis**.

COMMENT

In its present form, the sentence does not make reasonable sense. I assume that what is meant is "Estrogen replacement therapy reduces bone resorption and may retard, halt, or reverse loss of bone mineral." However, this must be supported by appropriate date in the Clinical Pharmacology Section. Decision on this is deferred for the present; see discussion below.

2. Under **Clinical Pharmacology**, a new subsection **Clinical Studies**, has been added. This is purported to incorporate the results from the PEPI trial regarding increase of bone mineral density in patients receiving estrogen therapy.

COMMENT

The proposed wording and accompanying table is not a balanced summary of the data in the supporting journal article.

a) The statement and table refer to"adherence" to therapy. I assume this refers to "completers"; the data should be based on "intent to treat" and should include actual numbers of subjects in each group.
b) The numbers in the table of "n" are not meaningful; they should be expressed as "n" for each cell.
c) Although the text states that the differences between placebo and estrogen were "significant," only a point value is given (and this is different for the placebo patients in the table and text) with no parameters allowing evaluation by the physician of the range or statistical validity of the differences. Furthermore, without knowledge of the baseline BMD values, the clinical significance of these differences cannot be ascertained.
d) There is a statement concerning differences between "older" and "younger" women in response to ERT; no values are given, no evidence of variability, no definition of "older" and "younger."

3. A sentence in the **Patient Information** sheet has been changed based on the PEPI report. Comment on this is deferred until appropriate wording is approved for the labeling.

4. **CONCLUSION:** The suggested changes in submitted Draft labeling are not approvable. Please transmit sections 1, 2, and 3 above to the Sponsor for consideration in rewriting.

/S/

Leo Lutwak, M.D., Ph.D.
Medical Officer
December 12, 1997

/S/

Gloria Troendle, M.D. 12-15-97
Team Leader

CC: NDA Arch. NDA 4-782
HFD-580/Div. Files
HFD-510/Div. Files
HFD-580/DMoore
HFD-510/GTroendle/EGalliers/LLutwak
HFD-510/ Consults (+ request)
HFD-510/ Bone Drugs subject files (+ consult)

Medical Officer's Review of NDA Submissions

NDA #	4-782	Submission Dates:	10/26/95, 11/28/95
Drug:	Premarin Tablets	Dates Received:	10/30/95, 11/29/95
Sponsor:	Wyeth Ayerst Laboratories	Date Review Completed:	4/15/96

General Information

Name of drug

Generic name: Conjugated Estrogens, USP
Trade names: Premarin Tablets

Pharmacologic Category: Oral estrogen

Approved Indications:

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 and Route of Administration:

Solid tablet for oral administration, marketed in 0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg, and 2.5 mg strengths.

Related Drugs:

Generic formulations of conjugated estrogens tablets were previously approved and marketed by various ANDA sponsors from the 1970s to 1991, when CDER withdrew all ANDA approvals due to the pharmacokinetic finding that the generic formulations had rapid absorption rates compared with Premarin's modified release characteristics. ANDAs pending in OGD for reformulated conjugated estrogens products which contain 3 newly USP-designated concomitant components (17α-dihydroequilin, 17β-dihydroequilin, 17α-estradiol) in addition to their USP-specified active ingredients estrone sulfate and equilin sulfate.

Material Reviewed

October 26, 1995 submission:

Summary report of a clinical study entitled "Pilot Study on the Clinical Effects of Δ8,9-dehydroestrone Sulfate (DHES)" – conducted without benefit of an IND – by Drs. B. Bhavnani and D. Cicutti at St. Michael's Hospital, Toronto, Canada.

This study ("Canadian study") was a single-center, 8-week, single dose-level, uncontrolled, open-label trial of daily DHES 0.125 mg/day administered by oral capsule to 10 postmenopausal women. Although the report states that the administered dose is equivalent to the amount of DHES present in a 2.5 mg Premarin tablet, no chemistry, manufacturing, and controls information is given about the study drug composition or formulation. The nonsmoking subjects were selected by age (35-60 years), weight (within 15% of IBW), estradiol levels (<20 pg/ml), FSH levels (>50 mIU/ml), general good health, and postmenopausal status, defined as either surgical (due to benign pathology with bilateral oophorectomy) or physiological (spontaneous cessation of menses for one year). Study procedures consisted of a 30-day washout of prior prescription drug treatment followed by

daily study drug dosing and serial blood and urine sampling. Blood was collected on day 0 (predose), and on treatment days 1, 7, 14, 21, 28, 42, 49 and 56; samples were analyzed for changes in FSH, LH, SHBG, CBG, total cholesterol, HDL-C, LDL-C, triglycerides, conjugated diene production, lipid oxidation time, and oxidized LDL (T-bars). Urine was collected on day 0 (predose) and at treatment weeks 2, 3, 5, 6, 7 and 8; samples were frozen and analyzed using an ELISA for n-telopeptides, with values standardized for creatinine clearance. All plasma, serum, and urine samples were reportedly analyzed "in a blinded manner".

Reported results: (rounded to 2 significant figures by MO reviewer)

Study Population:

Of 10 enrolled subjects, 3 failed to meet entrance criteria ("reported FSH levels in excess[1] of 50 mIU/ml" for 3; reported estradiol level > 20 pg/ml for 1 of the 3), and one was lost to follow-up after predose sampling, yielding 6 subjects who completed the study (60%). All results are reported for these 6 subjects only.

Plasma Hormone and Hormone Binding Protein levels

FSH plasma levels:

Consistently decreased from baseline in all subjects by an average of 20% ($p=0.02$).

CBG levels:

Rose an average of 25% over baseline ($p=0.03$).

LH/SHBG levels:

No significant changes were observed.

"Markers of Cardiovascular Effects"

Lipid oxidation time (lag phase):

A significant 92% increase from baseline was observed ($p=0.04$).

Total cholesterol, triglycerides:

No significant changes from baseline were observed.

LDL-C, HDL-C, modified LDL (T-bars), and conjugated dienes (steady state levels):

No significant changes from baseline were observed.

"Markers of Bone Turnover"

Urinary n-telopeptide excretion:

Decreased from baseline, in 5 of 6 subjects, by a mean of 33.5% ($p=0.03$).

Results Not Reported

ApoA, ApoB, ApoE, urinary pyridinium crosslinks:

Due to incomplete analyses when the summary report was prepared, results will reportedly be submitted when available.

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[1]Despite the fact that FSH levels greater than 50 mIU/ml were required for enrollment, the summary report cites "FSH levels in excess" of 50 mIU/ml as the basis for excluding three of ten enrolled subjects.

November 28, 1995 submission:
Summary report of a second clinical study entitled "Pilot Study on the Clinical Effects of Δ8,9-dehydroestrone Sulfate (DHES) in Comparison to Estrone Sulfate", conducted – also without benefit of an IND – by Dr. Edmund Baracat, Professor and Chair, Department of Obstetrics and Gynecology, at the Escola Paulista de Medicine, Sao Paulo, Brazil.

This study ("Brazilian study") was a single-center, 12-week, open-label, randomized, active-controlled, parallel trial of DHES 0.125 mg/day in comparison with estrone sulfate (E_1S) 1.45 mg/day and the combination of DHES 0.125 mg/E_1S 1.45 mg/day administered by oral capsules to 30 postmenopausal women (10 per group). Although the sponsor states that these dosages are equivalent to the amounts of DHES and estrone sulfate present, respectively, in a 2.5 mg Premarin tablet, no chemistry, manufacturing, and controls information is given about the study drug compositions or formulations. The nonsmoking subjects were selected by age (35-60 years), BMI (less than 27.5 kg/m^2), estradiol levels (<20 pg/ml), FSH levels (>50 mIU/ml), general good health, and postmenopausal status, defined as either surgical (due to benign pathology with bilateral oophorectomy) or physiological (spontaneous cessation of menses for one year). Study procedures consisted of a 30-day washout of prior estrogen/progestin treatment followed by daily study drug dosing, with diary monitoring and serial blood and urine sampling. Prohibited concomitant medications included alcohol, estrogens, progestins, androgens, tibolone, lipid-lowering drugs, dopaminergic/antidopaminergic drugs, clonidine, digitalis preparations, anticonvulsants, and regular psychotropic, narcotic analgesic, or antihistamine usage.

Efficacy evaluation: "All analyses" were reportedly conducted "in a blinded manner".

- Diary cards:
  Subjects recorded and qualitatively scored (absent, mild, moderate, intense) nonspecific symptoms, including hot flushes, headache, dizziness, insomnia, palpitations, depression, nocturnal awakenings, irritability, vaginal dryness, and vaginal bleeding. Methods for baseline assessment were not described.

- Fasting blood samples:
  Collected days -1, 0 (predose), and 2-3 hours post-dose on days 1, 7, 14, 21, 28, 42, 56, 84; Analyzed for 17β-estradiol, LH, FSH, PRL, SHBG, CBG, total cholesterol, HDL-C, LDL-C, and triglyceride levels by Endocrine Sciences Laboratory, Agoura Hills, CA.

- First void urine:
  Collected daily days -1 to 84, stored frozen; Analyzed for N-telopeptide levels at Regional Bone Center, Helen Hayes Hospital, West Haverstraw, NY.

Safety evaluation:

- Medical, gynecologic, and laboratory exams @ screening and study completion:
  Hematological, biochemical, renal, hepatic, "cardiovascular", urinalysis profiles.

- Additional lab exams @ screening only:
  "Cardiovascular profile", HIV, hepatitis B determinations, Pap smears, mammography, urinary drug screens.

Statistical analysis:

All analyses of the 6 hormone parameters, 4 lipid parameters, and the urinary bone marker data were based on % change from baseline for each subject at each time point. Baseline values were calculated as the mean of day -1 and day 0 values. For each treatment group, t-tests determined whether the mean % change was significantly different from zero, at a 5% level of significance. ANOVA, based on % changes from baseline, was used for an overall comparison of the 3 treatment groups; if significant, then each of the 3 possible pairwise comparisons was done using the least significant difference procedure ("protected LSD procedure") by time point. A repeated measures ANOVA was also done for evaluation of time effect and time x treatment group interaction. For "several" (unspecified) parameters, actual changes from baseline were analyzed, with results reportedly similar for the two methods.

Hot flush data were analyzed based on actual changes instead of % changes, using paired t-tests for within-group analysis of changes from baseline. ANCOVA, with baseline value included as a covariate, was used to compare among the 3 treatment groups (allowing for adjustment for baseline differences), and pairwise comparisons were done using the protected LSD procedure. Analyses were done for the number of flushes, the severity of flushes, and a total score calculated for each subject. Weights of 1, 2, and 3 were assigned to mild, moderate, and severe flushes, respectively; the number of flushes was multiplied by their respective weights; the three subtotals were added to give an overall severity score (taking both number and severity into account), which was then divided by the number of flushes to yield an average severity score for each subject. Subgroup analysis of hot flush number was also conducted including only those subjects with seven or more flushes per day at baseline.

Reported results:

Study Population:

Of 30 enrolled subjects, all completed the study.
No emergencies or serious adverse reactions were reported.

Vasomotor Symptoms:

Baseline:

Baseline values represent the "mean scores obtained during the [unspecified] pretreatment evaluation period". No statistically significant differences were observed between the 3 groups for number, severity, or total hot flush score at baseline.

Hot flush number:

At 8 weeks (day 56), hot flush number decreased to near 0 in all treatment groups, with no significant differences observed between treatments. At 12 weeks (day 84), hot flush number decreased 98%, 93%, and 100% from baseline with DHES, E_1S, and combination DHES/E_1S treatment, respectively.

Subgroup analysis of subjects with at least 7 flushes/day at baseline reportedly indicated that 5 women in each group met that criterion, with an average of 9.4, 10.6, and 8.7 episodes per day (not significantly different from one another) for the DHES, E_1S, and combination DHES/E_1S treatment groups, respectively. In this analysis, hot flush number decreased 95%, 88%, and 100% from baseline at 8 weeks, and 98%, 89%, and 100% from baseline at 12 weeks with DHES, E_1S, and combination DHES/E_1S treatment, respectively.

Hot flush severity:

At 12 weeks, significant reductions were reported in mean severity scores with all treatments: from 1.71 (baseline) to 0.1 with DHES; from 2.06 to 0.3 with E_1S; and from 1.58 to 0 with combination DHES/E_1S, without significant differences between treatments. Hot flush total scores also declined significantly by 8 weeks with all 3 treatments. No subgroup analyses were performed for these data.

Plasma Hormone and Hormone Binding Protein levels

Gonadotropins and Prolactin:

FSH: Baseline levels were elevated in all treatment groups (average over 100 mIU/ml), without significant differences between groups. All treatments resulted in progressive, significant ($p < 0.005$) 40-50% declines by week 12.

LH: Levels declined with the 3 treatments, but less and more slowly than FSH, and reached statistical significance in the DHES group only.

PRL: Levels remained within the normal range throughout the treatment period in all groups, with sporadic % changes from baseline.

Estradiol:

Serum E_2 levels were less than 10 pg/ml at baseline in all 3 groups and rose to a steady range of 80-100 pg/ml after E_1S or the combination treatment. E_2 levels measured in the DHES group (50-60 pg/ml by 12 weeks) are reported to represent cross-reactivity in the radioimmunoassay with 17β-DHES, which the sponsor states is the major human metabolite of DHES. Assays conducted at Wyeth-Ayerst using HPLC and calibrated standards will be reported separately in a future report.
[Sponsor states they reveal that 17β-estradiol levels are very low in the DHES-treated women, remaining within baseline levels, while values for 17β-DHES are high after treatment, with unconjugated 17β-DHES said to reach about 80 pg/ml in this group.]

Serum Binding Globulins:

SHBG: Levels more than doubled after E_1S or the combination, with changes reaching persistent statistical significance within 2 weeks of treatment initiation. Levels rose 15-20% over baseline after DHES treatment, reaching statistical significance at 2-6 weeks.

CBG: Levels increased a consistent, significant 20-40% over baseline with all treatments, without significant differences between treatments.

Serum Lipids

Total cholesterol:

Levels decreased at 4 and 8 weeks in the E_1S and combination groups but returned toward baseline by week 12. Levels were not significantly changed from baseline at any time point in the DHES group.

HDL: Levels rose transiently over baseline in all treatment groups (maximum 10% in DHES and combination groups, maximum 20% with E_1S alone), but returned to baseline by week 12 in all treatment groups.

LDL: Levels showed a significant sustained reduction from baseline of 10-20% in the combination group. A similar trend observed with E_1S reached statistical significance at 4 and 8 weeks but not at 12 weeks. DHES treatment did not affect LDL levels at any time point.

Markers of Bone Turnover

N-telopeptide:

Urinary excretion was measured at baseline (pre-dose days -1 and 0) and at 8 weeks (56 days) on treatment. At baseline, no significant between-group differences were observed in the two separate samples. At week 8, urinary excretion was significantly and comparably suppressed 30-40% from baseline levels by all 3 treatments.

Clinical Background

FDA has been petitioned by Wyeth-Ayerst 11/30/94 (94P-0429 CP1: Citizen Petition to Establish the Proper Composition of Conjugated Estrogens and Conjugated Estrogens Tablets; and 94P-0430 CP1: Petition for Stay of Action - Approval of ANDAS for Conjugated Estrogens Products Not Containing DHES) not to approve any generic formulation of Conjugated Estrogens unless it contains specific quantities of DHES, a minor estrogenic component of Premarin which has never been required by USP monograph to be a constituent of Conjugated Estrogens, USP. Scientific aspects of this matter were discussed at a joint public meeting of the Fertility and Maternal Health Drugs Advisory Committee with Endocrinologic and Metabolic Advisory Committee and Generic Drugs Advisory Committee representation, held July 27-28, 1995.

Following presentations by pharmaceutical representatives, speakers invited by CDER, and members of the public, the joint Committee was asked several questions. When asked whether there is clinical evidence that significantly differentiates the efficacy of any approved estrogen from any other for approved indications (treatment of menopausal vasomotor symptoms and prevention of osteoporosis), the Committee unanimously responded in the negative. When asked the same question with reference to the safety of approved estrogens, the Committee unanimously stated that insufficient clinical data had been presented to permit making such a distinction. When asked whether other components of Premarin than estrone sulfate and equilin sulfate must be present in generic Conjugated Estrogens in order to achieve clinical efficacy and safety equivalent to Premarin, the Committee unanimously stated that insufficient data had been presented to determine whether or not any individual component of Premarin or any combination of components of Premarin other than estrone sulfate and equilin sulfate must be present in order for Premarin to achieve its established levels of efficacy and safety.

CDER is currently evaluating the petition in light of these recommendations and all available data bearing on this question. Refer to Proceedings of the Fertility and Maternal Health Drugs Advisory Committee, July 27-28, 1995, for details of the public discussion.

Summary and Evaluation

Summary reports are submitted of two pilot studies conducted by Wyeth-Ayerst to determine the clinical effects of DHES in postmenopausal women and to demonstrate that DHES "is a potent estrogen with unique properties" (page 22, 11/29/95 submission). Based on "previously submitted in vitro studies, in vivo laboratory animal studies, clinical data, and" the results of these pilot studies, the sponsor concludes that:

1) DHES "has been demonstrated to be an active estrogen with tissue- and system-specific effects"; and thus

2) DHES "represents a likely contributor to the overall clinical effects resulting from Premarin administration" (cover letter, 11/29/05 submission).

In contrast, this reviewer does not find the Canadian and Brazilian pilot study findings supportive of these conclusions because of serious deficiencies in the design of both studies:

1) The dose of DHES evaluated in both studies is in excess of 4 times the amount of DHES in a standard clinical dose of 0.625 mg Premarin.

Since any estrogenic compound will produce predictable effects on estrogen-responsive target tissues if a large enough dose is administered (as unanimously agreed by the joint Advisory Committee, see *Clinical Background* above), the Brazilian study findings (suppression of gonadotropin secretion and n-telopeptide excretion, stimulation of binding protein concentrations with high-dose DHES administration) simply confirm that DHES is an estrogen. They cannot be extrapolated to the usual clinical situation in which DHES is administered at less than 4% of a mixture of 10 or more estrogens in Premarin (a DHES

dose less than one-fourth of that administered in the Brazilian study). This point was clearly stated by the joint Advisory Committee in response to the sponsor's public presentation of the pilot study data (refer to Proceedings of the Fertility and Maternal Health Drugs Advisory Committee, July 27-28, 1995). Clinically significant estrogenic effects have never been demonstrated with DHES administration at its usual clinical dose (i.e., 3-4% of Premarin 0.625 mg, or roughly 0.021 mg/day DHES).

2) No chemistry, manufacturing, and controls information is provided about the dosage forms used in the clinical studies.

Since equine estrogens are vulnerable to oxidative and hydrolytic degradation under warm, moist, or acidic conditions, the composition of the study drug dosage forms may have changed over time. Without this information, the purity of the administered drugs and their excipient content cannot be assessed and no reliable conclusions can be drawn about the relationship of specific drug ingredients to observed clinical or biochemical outcomes.

3) The Canadian and Brazilian studies lacked placebo control groups.

Because vasomotor symptoms are highly responsive to placebo treatment, the observed suppression of hot flushes in the Brazilian study cannot necessarily be attributed to drug effect. Without placebo control and blinded drug administration, the subjective vasomotor symptom outcomes could be due to placebo response, especially in subjects with only mild symptoms at baseline. In the subgroup with frequent baseline vasomotor symptoms, findings were only reported for the endpoint of hot flush number, not severity; thus, even in this group the outcomes could be largely due to placebo response.

4) The summary study reports lack essential details needed for a proper evaluation of their results.

For example, neither study protocols nor case report forms are submitted. Thus, reported baseline hot flush rates cannot be confirmed because the baseline period for hot flush monitoring and methods used are not described.

Notwithstanding these significant deficiencies, one consistent outcome does emerge from the Brazilian study report. In spite of the high DHES dose administered and its apparent estrogenic effects with single-agent administration, these "DHES effects" never augment the observed effects of estrone sulfate when administered in combination with it. Thus, although the DHES/E_1S treatment group received only 2 of the 10 or more identified estrogens in Premarin, the Brazilian study certainly does not suggest that DHES contributes any independent or additive effect to the clinical estrogenic effects of E_1S alone. Thus, even if single-agent DHES (at doses present in currently marketed Premarin) possessed clinically significant estrogenic activity in human subjects (which has not been shown by the submitted data), the Brazilian study findings suggest that such estrogenic activity would be completely masked by the clinical effects of the estrone sulfate present when both are administered together as components of Premarin.

In summary, the submitted clinical reports are claimed to demonstrate that DHES is "an active estrogen" and "a likely contributor to the overall clinical effects resulting from Premarin administration." However, due to significant deficiencies in the design of the two studies as well as incomplete reporting of their chemistry, clinical protocols, and results, no conclusions can be drawn from these reports about the potential clinical effects of DHES as administered in Premarin. Because the two pilot studies provide the first clinical data on DHES administration to women, however, their very limited findings are nonetheless of interest in view of the pending Citizen Petitions. Other than failing to suggest additive estrogenicity compared with estrone sulfate, however, their findings are unevaluable.

Recommendations

The submitted summary reports of two pilot studies on the clinical effects of DHES in postmenopausal women contain data that are unevaluable for the scientific determination of whether DHES should be a required component of Conjugated Estrogens, USP. As such, it is recommended that their reported results not be considered supportive of the pending Citizen Petitions #94P-0429 and 94P-0430, which request that DHES be regulated as if it were a therapeutically active ingredient of Premarin.

/S/ 4/19/96

Linda J. Golden, M.D. Date
Medical Officer

P. Corfman 96.04.25.

cc: Original NDA Arch
HFD-510
HFD-510/PCorfman/LRarick/SSobel/YYChiu/SMoore/LGolden/CKish
HFD-604/WAdams
HFD-003/RWilliams/JMolzon

JAN - 4 1996

Medical Officer's Review of NDA SE-2 Efficacy Supplement Submission

NDA #	4-782/S-093	Submission date:	6/19/95
MOR #	2	CDER Receipt Date:	6/21/95
Sponsor:	Wyeth Ayerst Laboratories	Date Review completed:	12/28/95

General Information

Name of drug

Generic: Conjugated estrogens;

Trade: Premarin Tablets, USP;

Chemical: Sodium estrone sulfate and sodium equilin sulfate.
Also contains as concomitant components 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin.

Pharmacologic Category: Oral estrogen;

Approved indications:

1. Moderate to severe vasomotor symptoms associated with the menopause.
2. Atrophic vaginitis.
3. Osteoporosis (loss of bone mass).
4. Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.
5. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.

Dosage form and route of administration:

Oral tablet with modified release characteristics.

Related drugs:

Conjugated estrogens tablets; Esterified estrogens tablets;
Micronized estradiol (tablets, transdermal patch);
Piperazine estrone sulfate tablets; Ethinyl estradiol tablets.

Clinical Background

This efficacy supplement, which was originally submitted 2/15/94 and found approvable 2/17/95, proposes a labeling change under the "Dosage and Administration" section for indicated treatment of female hypogonadism. Based upon published literature, the sponsor proposed to reduce the dosing recommendation from 2.5 mg to 7.5 mg daily to 0.3 mg to 1.25 mg administered cyclically. The current labeling recommendation was historically based on earlier literature and the DESI review, while more recent literature suggests that lower doses are sufficient to provide the benefits of estrogen therapy in this population.

On 2/22/95, an approvable letter was sent to the sponsor which noted numerous labeling inconsistencies with the current (August 1992) Labeling Guidance for Estrogen Drug Products. In addition, the published clinical data submitted to support the revised dosing recommendations was found to support recommended dosing at an even lower level – 0.15 mg/day to 0.625 mg/day – than the 0.3 mg to 1.25 mg/day proposed by the sponsor.

In keeping with the principle that the lowest effective dose should be utilized to minimize the toxicity of chronic estrogen replacement therapy, the sponsor was advised that adequate justification had not been provided for chronic doses higher than 0.625 mg/day. Despite this, the lack of available (a) dose-ranging bone density data in skeletally mature Turner's syndrome patients and (b) epidemiologic data on fracture risk in this population was noted, which precludes definitive determination of the potential need for higher doses than 0.625 mg to assure optimal bone mineralization in these patients. The sponsor was advised (a) that the labeling should include a summary of the available pharmacodynamic data on Premarin treatment of delayed puberty, and (b) to consider conducting a future adequate dose-ranging trial (using state-of the-art bone density endpoints) of higher Premarin doses in skeletally mature hypogonadal patients.

The current submission amends supplement S-093 to provide revised draft labeling, based on both the 1992 Labeling Guidance for Estrogen Drug Products and the currently approved labeling for PREMPRO and PREMPHASE (NDA #20-527, approved 11/17/95). The draft labeling contains revisions to the Clinical Pharmacology (re: lipid effects), Warnings (re: breast cancer findings from PEPI) , Precautions (re: uterine fibroids and hypocalcemia), and Information for the Patient (re: Uses of Estrogens and lipid effects) sections. If approved, the submitted labeling will supersede all of the following pending supplemental applications: 82-ope

S-096 (lower dosing recommendations for treatment of vasomotor symptoms under the DOSAGE AND ADMINISTRATION section).

Labeling Review

Description

Refer to Chemistry Review. Appears acceptable to this reviewer as revised.

Clinical Pharmacology Acceptable as revised, except as follows:

Indications and Usage — Acceptable as revised, except as follows:

Contraindications — Acceptable as revised.

Warnings

BOXED WARNING: — Acceptable as revised.

WARNINGS: — Acceptable as revised, except as follows:

Precautions — Acceptable as revised, except as follows:

Information for Patients

Introduction (section entitled "Estrogen Drugs" in draft labeling): Acceptable as revised.

BOXED WARNING: Acceptable as revised.

Section entitled "Uses of Estrogen": Acceptable as revised, except as follows:

Section entitled "When Estrogens Should Not Be Used": Acceptable as revised.

Section entitled "Risks of Estrogens": Acceptable as revised, except as follows:

Section entitled "Reducing Risk of Estrogen Use": Acceptable as revised.

Section entitled "Other Information": Acceptable as revised, except as follows:

Adverse Reactions	Acceptable as revised.
Dosage and Administration	Acceptable as revised, except as follows:

Summary and Evaluation

1. The revised dosing recommendations for the treatment of female hypogonadism are now acceptable, provided the order of the second and third paragraphs under this indication are reversed, as noted above.

2. The revised draft labeling is now consistent with the 1992 Labeling Guidance for Estrogen Drug Products, except where specifically cited above. All remaining inconsistencies detailed above should be corrected prior to approval of this labeling supplement.

Recommended Regulatory Action

1. This supplement is approvable provided all labeling revisions detailed above are implemented. The sponsor should be requested to submit revised draft labeling incorporating all recommended changes for review prior to final approval of this supplement.

2. As previously recommended, it is important to determine whether higher Premarin doses than 0.625 mg are needed for skeletal support in this chronically estrogen-deficient population; the sponsor should thus be encouraged to conduct an adequate dose-ranging trial (using state-of the-art bone density endpoints) of higher Premarin doses in skeletally mature hypogonadal patients.

/S/ 12/29/95

Linda J. Golden, M.D. Date
Medical Officer

P. Corfman 1.4.96.

Attachments: 1992 Labeling Guidance for Estrogen Drug Products
Approved labeling for PREMPRO/PREMPHASE (11/17/95, NDA #20-527)

cc: Original NDA Arch
HFD-510
HFD-510/SSobel/LRarick/PCorfman/LGolden/CKish

Kish

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Medical Officer's Review of NDA SE-2 Efficacy Supplement

NDA #	4-782/S-093	Original submission date:	2/15/94
MOR #	1	User Fee Goal Date:	2/22/95
Sponsor:	Wyeth Ayerst Laboratories	Date Review completed:	2/17/95

General Information

Name of drug

Generic: Conjugated estrogens;

Trade: Premarin Tablets, USP;

Chemical: Sodium estrone sulfate and sodium equilin sulfate.
Also contains as concomitant components 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin.

Pharmacologic Category: Oral estrogen;

Approved indications:

1. Moderate to severe vasomotor symptoms associated with the menopause.
2. Atrophic vaginitis.
3. Osteoporosis (loss of bone mass).
4. Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.
5. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.

Dosage form and route of administration:

Oral tablet with modified release characteristics.

Related drugs: Conjugated estrogens vaginal cream and injectable formulations, Esterified estrogens tablets, Micronized estradiol (oral tablets, vaginal cream, and transdermal patch), piperazine estrone sulfate (oral tablets and vaginal cream), Ethinyl estradiol tablets.

Clinical Background

The purpose of this efficacy supplement is to provide for a labeling change under the "Dosage and Administration" section for the treatment of female hypogonadism. Based upon recent published literature, the sponsor proposes to reduce the dosing recommendation from 2.5 mg to 7.5 mg daily to 0.3 mg to 1.25 mg administered cyclically. The present labeling recommendation was historically based on earlier literature and the DESI review. Recent literature suggests that lower doses are sufficient to achieve the benefits of hormone therapy in this population.

Literature references submitted in support of the sponsor's proposed labeling change:

1. Kulin HE, Reiter EO: Managing the patient with a delay in pubertal development. The Endocrinologist 1992; 2:231-239.

This clinical review considers the diagnostic evaluation of delayed puberty, indications for treatment, and therapeutic alternatives for each etiologic disorder.

The section entitled "Suggested Therapeutic Approach" states:

"The aim of sex hormone therapy for the boy or girl of pubertal age is to promote secondary sex characteristics and normal linear growth."
"The secondary sex characteristics of importance are breast development, penile size, and pubic hair."
"The primary side effect to be avoided in the initiation of puberty is an acceleration of bone maturation in excess of chronologic age."
"The underlying dictum of treatment is to use as little replacement hormone as possible. Remarkably small amounts of steroid are needed to promote growth and the onset of secondary sex characteristics."

The section entitled "Long-Term Sex Hormone Replacement Therapy" states:

"Oral therapy with the estrogens...is recommended in the female."
"The dose should be the lowest that provides the desired effects."
"Treatment can be started with low daily doses of estrogen (Premarin 0.15 mg) or ethinyl estradiol (2 to 5 μg) for approximately 1 year. After an initial period of breast and uterine stimulation, the continuous estrogen dose is doubled and carried on for another 6 to 12 months. Estrogen plus progesterone is then employed cyclically to produce monthly vaginal bleeding."
"All efforts should be made to initiate replacement at the expected time of puberty, certainly by the age of 11 to 12 years."

2. Maruca J, Kulin HE, Santner SJ: Perturbations of negative feedback sensitivity in agonadal patients undergoing estrogen replacement therapy. J Clin Endocrinol Metab 1983; 56:53-59.

In this cross-sectional study of 30 females with gonadal dysgenesis, ages 2 months to 17 years, urinary gonadotropin measurements were employed to quantify FSH and LH levels during childhood and during pubertal induction by the administration of exogenous sex steroids. Karyotypes included Turner's syndrome (45,XO, n=16), Turner's syndrome variants (n=4), various mosaic patterns (n=7), 46,XY (n=2), and a monosomic X cell line (n=1).

Eighteen of these patients, aged 11 3/12 to 16 11/12, were followed during initial estrogen replacement (instituted individually when clinically indicated) with Premarin at either 0.15 mg (n=7), 0.3 mg (n=5), or 0.6 mg (n=6) orally per day as a single morning dose. At 3 month intervals, patients were assessed for blood pressure, secondary sex characteristics, height, and urinary gonadotropin levels. Bone age was determined, by the method of Greulich and Pyle, at initial presentation, at onset of estrogen therapy, and yearly thereafter. After 1-2 years of continuous daily Premarin treatment at the initial dose level, the dose was gradually increased to 0.3 or 0.6 mg, with the eventual addition of "cyclic progesterone and estrogen".

Significant findings included the following:

1. When related to bone age, urinary FSH was always elevated before age 3 years and after the age of 9 years, based on 68 timed urine samples from 29 patients with gonadal dysgenesis in whom specimens were obtained before exogenous estrogen exposure, and compared to 48 normal females with bone ages of 0 to 14. LH was less consistently abnormal, being increased in 74% of specimens from patients with bone ages of 9-14.

2. In the absence of a functioning gonad, maximum FSH excretion at adult castrate levels occurred by bone age 10 years and that for LH occurred by bone age 11 years. By contrast, normal girls took considerably longer to reach gonadotropin measurements well within the intact adult range.

3. After initiation of Premarin treatment (0.15, 0.3, or 0.6 mg/day) in 17 patients not previously exposed to estrogen, FSH and/or LH levels were suppressed within 3 months to nadir levels within or very close to the normal prepubertal range in 5/5 patients on 0.6 mg, in 4/5 patients on 0.3 mg, and in 2/7 patients on 0.15 mg. Urinary gonadotropin levels remained suppressed for 8-26 months, then escaped from suppression in all patients (with return to pre-treatment levels), despite continuation of Premarin treatment.

4. After dosage escalation in 9 patients previously exposed to Premarin, urinary gonadotropin levels failed to suppress into either the normal prepubertal or the normal adult ranges in 3/4 girls receiving 0.3 mg (after prior treatment with 0.15 mg for 14-22 months) and in 2/5 girls receiving 0.6 mg (after prior treatment with 0.3 mg for 13-33 months).

5. Serial bone age determinations in 25 agonadal patients of chronological ages 9-17 years revealed that in the absence of estrogen treatment, bone maturation advanced at approximately 2/3 the rate of chronological age during the peripubertal years.

6. Premarin treatment accelerated bone maturation in a dose-dependent manner, with a mean ratio of bone age advancement to chronological age advancement of 1.1 in patients receiving 0.15 mg (n=6), a mean ratio of 1.5 in patients receiving 0.3 mg (n=5), and a mean ratio of 2.1 in patients receiving 0.6 mg/day.

7. Premarin treatment induced breast development in all patients receiving 0.3 or 0.6 mg/day, and in 6/7 patients receiving 0.15 mg/day. The one girl not responding to 0.15 mg had no breast development after a year's course of 0.3 mg/day and had hypoplastic nipples.

8. Withdrawal bleeding was uniformly inducible with cyclic estrogen and progesterone after 1 year or more of stimulation with 0.6 mg/day. By contrast, 5 patients receiving 0.3 mg/day for 1 to 2.5 years did not experience withdrawal bleeding after cyclic estrogen plus progesterone and required advancement to 0.6 mg Premarin.

The authors offer the following "preliminary guidelines" for the induction of secondary sex characteristics with exogenous sex steroids:

> "CE in a dose of 0.15 mg is associated with the appearance of breast development and a normal ratio of bone age increment to gain in chronological age. It seems reasonable to initiate puberty between ages 11-12 with such a regimen, and then to double the dose after 1-2 years of continuous estrogen therapy. Progesterone and estrogen (0.3-0.6 mg CE) can then be given in a cyclic fashion for the third year of therapy, resulting in the timely (age 13-14 yr) appearance of vaginal bleeding."

3. Schroeder SA, Tierney Jr. LM, McPhee SJ, Papadakis MA, Krupp MA, eds: Current Medical Diagnosis & Treatment, a LANGE medical book, 1992; chapters 13 (Gynecology & Obstetrics) and 20 (Endocrine Disorders).

For treatment of Turner's syndrome, this review of textbooks recommends "Replacement estrogen is begun at age 12 or 13 years with low doses of conjugated estrogens (0.3 mg) or ethinyl estradiol (5 μg) given on days 1-25 per month; the dose is gradually increased over 2-3 years to 0.625-1.25 mg of conjugated estrogens or 10-20 μg of ethinyl estradiol. Medroxyprogesterone acetate, 5 mg, is added on days 16-25 of the month to induce menses" (pp 896-897). No clinical data are referenced as the basis for these recommendations.

4. Shore RM, Chesney RW, Mazess RB, Rose PG, Bargman GJ: Skeletal demineralization in Turner's Syndrome. Calcif Tissue Int 1982; 34:519-522.

The bone mineral status of 17 girls with Turner's syndrome, ages 9.7 to 23.0 years, was evaluated by single photon absorptiometry (SPA), and eight of these subjects were followed longitudinally with 2 or more determinations made 3.2 +/- 1.7 years after their initial assessments. Bone mineral content (BMC) was determined at standard midshaft sites of the nondominant radius, ulna, and humerus, and compared with more than 800 healthy control children of ages 5-20 years. Based on these controls, sex-specific multiple regression formulas were established, normalized by age, height, weight, and bone width, to give predicted values for BMC for each bone. Measured BMC values were compared to that

predicted for the same bone to determine the percent deviation from predicted, and then averaged for the 3 bones to give the mean percent deviation from predicted, indicated as "BMC". To correct for delayed skeletal maturation, predicted values were also generated by using the subjects' skeletal age rather than chronologic age, but this analysis was limited to 9 Turner's syndrome subjects who had bone age determinations in close temporal proximity to their initial bone mineral studies. For these subjects, chronologic age was 15.3 +/- 2.9 years and bone age (by the method of Greulich and Pyle) was 12.1 +/- 1.5 years, for a bone age 3.1 +/- 1.2 years (95% confidence) less than chronological age.

Significant findings included the following:

1. Height for age and BMC were significantly below predicted ($p < 0.0001$).

2. When the estrogen-treated and untreated groups were compared, the estrogen-treated girls were older ($p < 0.005$) and had a greater height for age ($p < 0.005$) and BMC ($p < 0.05$).

3. For the 4 girls who were 14 years old or younger, the deficit found for BMC (-29.2 +/- 8.1%) was nearly identical to that of the entire group of 9 girls who were not receiving estrogens (-29.2 +/- 6.3%).

4. An apparent correlation was observed between age and BMC such that with advancing age there was relative improvement of the bone mineral deficit. Since the estrogen-treated girls were older than the untreated subjects, it was not possible to determine whether the improved bone mineral status was due to age or estrogen therapy, however.

5. For the 9 girls with bone age determinations in close temporal proximity to their initial bone mineral studies, their BMC calculated with chronologic age was -27.1 +/- 5.6, whereas when calculated by skeletal age it was -20.4 +/- 7.2. Thus, delayed skeletal maturation accounted for 25 +/- 8% (95% confidence) of the deviancy in BMC.

6. For the 8 girls followed longitudinally with bone mineral studies, the change in BMC was +0.8 +/- 4.5%, which was not significantly different from zero. No relationship was observed between the individual changes in BMC and estrogen treatment during this time.

The authors conclude that while BMC in Turner's syndrome was 25.4% below that predicted by age, sex, height, weight, and bone width, only 25% of the deviancy in BMC could be attributed to delayed maturation. Furthermore, although the 9 girls who were not receiving estrogens had significantly lower height for age and BMC than those who were being treated, it could not be determined whether these differences were due to estrogen treatment or merely reflected a trend toward relative improvement in bone mineralization with advancing age. Since the 4 girls who were 14 years or younger were as severely osteopenic as the older subjects in the estrogen-untreated population, the authors propose that the osteopenia of Turner's syndrome may not be due simply to estrogen deficiency, but may instead represent an independent effect of the chromosome constitution.

5. Tang GWK, Ma HK: Gonadal dysgenesis: A review of 15 years' management. Asia-Oceania J Obstet Gynaecol 1989; 15:11-16.

This retrospective review of 15 years of medical records from a Menstrual Disorder Clinic at the University of Hong Kong describes a total of 314 patients with primary amenorrhea of whom 119 were found to have gonadal dysgenesis. Clinical characteristics of the patients, diagnostic and therapeutic modalities are described. The authors state that "Premarin and Provera were used since 1975...[in] dose[s] of...0.625 mg daily and...5-10 mg daily for 21 and 7-10 day respectively." They further state that "their height...cannot be improved with oestrogen therapy."

6. Van Campenhout J, Choquette P, Vauclair R: Endometrial pattern in patients with primary oestrogenic amenorrhea receiving estrogen replacement therapy. Obstet Gynecol 1980; 56:349-355.

In this cross-sectional study, endometrial histologic patterns were reviewed in 38 patients receiving chronic hormone replacement therapy for primary amenorrhea: 27 of 42 total cases of gonadal dysgenesis, 9 of 25 cases of primary selective gonadotropin deficiency, and both of 2 cases of resistant ovary syndrome seen at Notre-Dame Hospital, Montreal, Canada, from 1965 to 1980. Of the cases reviewed, 3 had received unopposed estrogens for 2.5 to 10 years at the time of study (ethinyl estradiol 20 μg/day x 5 and 10 years, respectively, in 2 patients; conjugated estrogens 1.25 mg/day x 2.5 years in one patient). The remaining 35 patients had received cyclic sequential estrogen/progestin treatment with various combinations of estrogens (most patients received multiple drug regimens):

Ethinyl estradiol (EE):	50-100 μg/day x 1-8 years, n=24;
Mestranol:	40-80 μg/day x 1-11 years, n=25;
DES:	0.25-0.5 mg x 3-11 years, n=2; and/or
Premarin:	1.25 mg/day x 1-13 years, n=15;
	2.5 mg/day x 6 months, n=1;

and progestins:

Provera:	5-10 mg/day for the last 5-10 days of each 21 day cycle, n=26;
Norethindrone:	0.5 mg/day, n= 24; or 1-2 mg/day, n=4; for the last 7 days of a 21 day cycle of EE or mestranol;
Dimethisterone:	25 mg/day cycled sequentially with EE 100 μg/day, n=8; or
D-norgestrel:	0.25 mg/day cycled sequentially with EE 50 μg/day , n=1.

The mean duration of exposure to hormonal treatment was 7.9 years, with a range of 2 to 22 years. The patients' ages ranged 19 to 44 years, with a mean of 26.7 years. All patients were asymptomatic except 2 with metrorrhagia. These 2 and 2 others underwent cervical dilatation and endometrial curettage under general anaesthesia; the remaining 34 underwent outpatient endometrial biopsy with a Novak curette. All histopathology material was read by the same pathologist.

Significant findings included the following:

1. Cystic glandular hyperplasia without atypia was diagnosed in 3 patients with gonadal dysgenesis, 2 of whom had been taking unopposed ethinyl estradiol for 5 and 10 years respectively. The third patient developed focal cystic glandular hyperplasia in an otherwise normal proliferative endometrium after 12 years of treatment with Premarin 1.25 mg with Provera 5 mg x 5 days/cycle, followed by 2.5 years of treatment with mestranol 40 μg with norethindrone 0.5 mg x 7 days/cycle.

2. No atypical hyperplasia or carcinoma was diagnosed in this series of patients.

3. No correlation was noted between bleeding pattern and endometrial histology: of the 2 patients with metrorrhagia, one had endometrial hyperplasia and the other had normal proliferative endometrium, while the other 2 patients with hyperplasia had regular and normal withdrawal bleeding.

Based on these data and a review of published literature, the authors conclude that "daily doses of ethinyl estradiol, 25 μg; mestranol 40 μg; or Premarin, 1.25 mg, induce full proliferation of the endometrium." They further conclude that "all reported patients with endometrial carcinoma as well as the 25 patients [reported in published literature to that date] with endometrial hyperplasia have been treated for at least 4 years. Until the present conclusions are further substantiated, these patients should be closely watched by annual endometrial biopsy especially after 4 years of exposure to estrogen-progestogen replacement therapy."

7. Emans SJ, Grace E, Hoffer FA, Gundberg C, Ravnikar V, Woods ER: Estrogen deficiency in adolescents and young adults: Impact on bone mineral content and effects of estrogen replacement therapy. Obstet Gynecol 1990; 76:585-592.

In this prospective 2-year study, 35 adolescent and young adult women with estrogen deficiency (due to Turner's syndrome, n=12; radiation-induced ovarian failure, n=10; 46,XX ovarian failure, n=5; hypogonadotropic hypogonadism, n=5; anorexia nervosa, n=2; surgically-induced ovarian failure, n=1) self-selected treatment or non-treatment with Premarin 0.625 mg/d x 21 days and Provera 10 mg/day x days 12-21 each calendar month. These subjects, and 2 additional patients with Turner's syndrome (45,X0 and 45,X0/46,XX) but with normal gonadotropin and estradiol levels and normal menses, were evaluated at baseline and at 6 month intervals for medical/dietary/exercise/social history, physical exam, skinfold measurements, body mass index (BMI), Tanner staging, 3-day written food diary, serum gonadotropins, estradiol, cholesterol, HDL, triglycerides, antithrombin III, osteocalcin, spot urinary γ-carboxyglutamic acid, and bone density by single photon absorptiometry (SPA). The distal one-third of the radius was scanned to estimate cortical bone mineral content (BMC), bone width (BW), and bone density (BD), and the distal one-tenth of the radius was scanned to measure primarily trabecular bone as medullary BMC, medullary BW, and medullary BD. The z score was calculated as the number of standard

deviations above or below the mean for age, with reported precision of 1.4% for the distal one-third and 3.0% for the distal one-tenth of the radius. Dual photon absorptiometry (DPA) of the lumbar spine was performed at the end of the study in 25 patients (20 in the treated group, 3 in the untreated group, and the 2 estrogenized Turner's patients), with reported precision of 1.5-2.0% and with results compared with an age-matched control population.

Significant findings included the following:

1. All studied patients were Caucasian, none used anticonvulsant drugs or had hyperthyroidism at baseline. Other baseline findings included a mean Tanner stage of 4.3 +/- 1.1 for breast development and 4.0 +/- 1.5 for pubic hair, and all but 2 patients had reached final adult height and mature bone age at entry into the study.

2. For the 35 estrogen-deficient patients, individual variables found to be significant predictors for better baseline SPA bone density measurements included:
Age (for cortical BMC and BD, medullary BMC and its z score, and medullary BD and its z score);
History of spontaneous pubertal development (for medullary BW and its z score);
History of radiation therapy (for medullary BW and its z score); and
BMI (for cortical BMC and BW, medullary BMC and its z score, and medullary BW).

Estradiol levels, total previous estrogen dose (mg), spontaneous menarche, exercise score, and calcium intake did not contribute a significant R^2 for the SPA measurements.

3. Comparison of baseline bone densities of treated and untreated patients revealed that the (self-selected) non-treatment group had better initial bone density measures by SPA than the (self-selected) treatment group for cortical BMC and BW, for medullary BW, and for z scores for medullary BMC and BW. Women selecting the non-treatment group were also younger (mean 18.6 +/-3.7 years vs. 21.2 +/- 2.9 years in the self-selected treatment group), more likely to have had spontaneous pubertal development (90% vs. 36% of treatment group subjects), more likely to have had spontaneous menarche (80% vs. 8%), more likely to have had menses following menarche (70% vs. 8%), and less likely to have taken estrogen/progestin prior to study enrollment (20%) than were women who self-selected Premarin/Provera treatment (92%).

4. Among treatment group subjects, the baseline SPA values were more than 2 SDs below the mean for normative data in 64% of subjects for cortical BMC, in 44% for cortical BD, and in 60% for medullary BMC.

5. Over the 24 month study, the absolute values of cortical BMC and cortical BD remained stable in the Premarin/Provera-treated group (authors state these values showed a decrease which was not statistically significant, p.588). Because a gradual increase in BMC would be expected with increasing age in normal females, however, the z scores of cortical BW and BD deviated further below the mean for age during the study period.

6. Over the 24 month study, the Premarin/Provera-treated group showed a "small increase" in medullary BD, but not in the z score, and a "marginally significant increase" in the z score of medullary BMC.

7. Over the 24 month study, untreated patients had no statistically significant changes in cortical BMC, cortical BD, the z score of cortical BW, or any medullary bone parameters. Despite this finding, by 24 months, there were no differences in the mean SPA measurements between the Premarin/Provera-treated and untreated groups.

8. The 2 estrogenized Turner patients (and 3 patients' sisters) had SPA measurements in the normal range at all visits.

9. Serum lipid levels, antithrombin III levels, osteocalcin levels, and mean systolic and diastolic blood pressures were not statistically different in treated patients on or off Premarin/Provera therapy. The only predictor of serum cholesterol level was an inverse relationship to fiber intake. Mean urine levels of γ-carboxyglutamic acid were not significantly affected by Premarin/Provera treatment.

10. Although few patients were evaluated by DPA, DPA findings correlated with SPA findings on medullary BMC ($r = 0.42$) and its z score ($r = 0.42$). The mean vertebral DPA for treated and untreated patients was 0.99 +/- 0.11 g/cm^2, or 82 +/- 9% of the bone density value of an age-matched control population, while the 2 estrogenized Turner patients had normal DPA values.

11. Among all the variables examined for Premarin/Provera-treated patients, age was the only significant predictor of higher DPA bone density and a history of radiation predicted lower-than-normal DPA bone density.

Based on these findings, the authors conclude that "bone density measurements were influenced by age, BMI, history of spontaneous pubertal development, and radiation therapy." They note the limitation of their findings by the small number of subjects, the expected very small increments in cortical bone over 2 years, the precision of the SPA and DPA scanners, and the lack of randomization to treatment group. Despite controlling for baseline differences between groups in the statistical analysis, baseline differences of note included the increased likelihood that untreated patients had undergone spontaneous pubertal development and menarche compared to the treated patients. Untreated patients were thus likely to have started with higher bone density than the treated patients, in spite of 92% of the treatment group having already received estrogen therapy before the start of the study. Because the 2 endogenously estrogenized Turner syndrome patients had normal bone density measurements by both SPA and DPA, the authors suggest that estrogen deficiency in childhood and adolescence contributes to the abnormal bone density, in addition to chromosomally related structural differences.

8. National Academy of Sciences-National Research Council Drug Efficacy Study report on Premarin Tablets, Evaluation by the Panel on Drugs Used in Disturbances of the Reproductive System; report sent to Wyeth Ayerst by FDA Bureau of Drugs DESI Project Office, July 11, 1972.

   Evaluated "Effective" for indication of "Hypogenitalism", with the following comment: "The syndrome of female hypogonadism includes a deficiency of both estrogen and progestogen as well as a deficiency of ova production. Estrogen replacement is only effective for the estrogen deficiency component of the syndrome." Documentation consisted of a single reference: Hamblen, EC: The use of estrogens in obstetrics and gynecology. Clin Obstet Gynecol 1960; 3:1021-1031

Important information from related IND's and NDA's:

None submitted. NDA #20-303 for Wyeth Ayerst's PREMPHASE and PREMPRO were approved in 12/94, but the products have not yet been launched. When commercially available, PREMPHASE will provide an approved sequential combination estrogen/progestin regimen for chronic hormone replacement therapy. It is not currently labeled for this indication, but will certainly be used clinically in this population.

Clinical Studies

None submitted. The purpose of this supplement is to provide for a labeling change under the "Dosage and Administration" section for the treatment of female hypogonadism. Based on the submitted published literature pertinent to female hypogonadism, the sponsor proposes to revise the dosing recommendation from "2.5 mg to 7.5 mg in divided doses for 20 days followed by a rest period of 10 days duration" to read as follows: "0.3 mg to 1.25 mg daily, administered cyclically (e.g., 3 weeks on and 1 week off). Doses are adjusted depending on the severity of symptoms and responsiveness of the endometrium."

Labeling Review

The submitted draft labeling in support of this labeling supplement was reviewed with reference to the August 1992 revision of the Labeling Guidance Text for Non-Contraceptive Estrogen Drug Products. As detailed below, it contains numerous inconsistencies with the current Estrogen Labeling Guidance. These inconsistencies should be corrected prior to approval of the labeling supplement.

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Reviewer's Comments

Despite being based on small numbers of patients, the submitted references suggest that breast development is adequately initiated in hypogonadal patients with a dose of 0.15 mg/day and that bone maturation acceleration is dose-dependent, with ratios of bone age advancement (Δ BA) to chronological age advancement (Δ CA) as follows (Maruca et al, 1983):

Premarin dose (mg/day)	ΔBA/ΔCA
0.15	1.1
0.3	1.5
0.6	2.1

The references also suggest that daily doses of 0.3-0.6 mg are sufficient to accomplish withdrawal vaginal bleeding in hypogonadal patients after cyclic estrogen/progestin treatment (Maruca et al, 1983).

Although clinical trials in postmenopausal women have repeatedly shown that 0.625 mg/day maximally preserves bone mineral density (BMD) in hypoestrogenic postmenopausal women, the lowest effective Premarin dose to maximize BMD in young, skeletally mature hypogonadal females has not been systematically studied. Instead, a range of doses have been empirically utilized, with typical reported doses of 1.25 mg/day among 15 Canadian hypogonadal patients (Von Campenhout J et al, 1980), and 0.625 mg/day among 119 similar patients in Hong Kong (Tang GWK et al, 1989). Limited prospective data on the skeletal effects of the 0.625 mg/day dose suggest that it preserves, but does not necessarily increase, bone mineral density in this population after epiphysial closure has occurred (Emans SJ et al, 1990). However, age seems to correlate with bone mineral density and content in hypogonadal patients such that the bone mineral deficit shows relative improvement with advancing age with or without estrogen replacement therapy (Shore R et al, 1982; Emans SJ et al, 1990). Thus, other factors than estrogen appear to participate in the progressive mineralization process in these patients.

One could speculate that the skeletal effects of Premarin may differ in postmenopausal and hypogonadal young women, such that Turner's syndrome patients in particular may require higher Premarin doses to optimize bone density and prevent osteoporotic fracture. On the other hand, the anti-resorptive action of estrogen replacement could be maximally effective only in bones which have already achieved their peak mineral content (i.e., postmenopausal women), and insufficient at any dose to promote maximal bone mineralization in growing bones. In the latter case, higher Premarin doses could simply cause additional toxicity without increased efficacy in hypogonadal patients, as appears to be the case for postmenopausal women. Without adequate dose-ranging bone density data in Turner's syndrome patients, one simply cannot determine whether or not a higher dose than 0.625 mg would provide better skeletal efficacy for these patients. This supplement cites no epidemiologic evidence of an increased long term fracture risk in hypogonadal females on Premarin 0.625 mg/day (indeed, this reviewer is not aware of any epidemiologic studies of fracture risk in this population, with or without estrogen replacement therapy). Thus, to date, data are unavailable to determine whether the reduced bone mineral density in these patients is clinically significant.

Because of these considerations, this reviewer believes that 0.625 mg is the highest dose that should routinely be recommended for chronic replacement in hypogonadal patients, based on the currently available data. It is important to determine in the future whether higher doses are in fact needed for skeletal support in this chronically estrogen-deficient population. Thus, the sponsor should be encouraged to conduct an adequate dose-ranging trial of higher Premarin doses in young hypogonadal patients to determine whether enhanced skeletal efficacy may offset the expected enhanced toxicity associated with chronic higher dose treatment.

For labeling purposes, the dosage and administration section should include a summary of the available pharmacodynamic data on Premarin treatment of delayed puberty. Thus, it is recommended that text be added to include the following information:

Conclusions

1. The sponsor has submitted sufficient published data to support their proposal to reduce the labeled dosing recommendation for the treatment of female hypogonadism from the current recommendation of mg daily to new dosing recommendations (see 2., below).

2. The submitted clinical data support dosing recommendations in the range of mg/day to mg/day rather than mg/day, as proposed by the sponsor.

   In keeping with the principle that the lowest effective dose should be utilized to minimize toxicity in chronic estrogen replacement therapy, the submitted clinical literature provides no adequate justification for chronic use of doses higher than 0.625 mg/day. However, the lack of available dose-ranging bone density data in skeletally mature Turner's syndrome patients, and the lack of epidemiologic data on fracture risk in this population, preclude a definitive determination of whether Premarin doses higher than 0.625 mg may be needed for optimal bone mineralization in these patients.

3. The submitted draft labeling in support of this supplement contains numerous inconsistencies with the current Labeling Guidance Text for Non-Contraceptive Estrogen Drug Products, as detailed above. These inconsistencies should be corrected prior to approval of this labeling supplement.

Recommended Regulatory Action

1. This supplement is approvable provided all labeling revisions detailed above are implemented. The sponsor should be requested to submit revised draft labeling incorporating all recommended changes for review prior to final approval of this supplement.

2. Since it is important to determine whether higher Premarin doses than 0.625 mg are needed for skeletal support in this chronically estrogen-deficient population, the sponsor should be encouraged to conduct an adequate dose-ranging trial (using state-of the-art bone density endpoints) of higher Premarin doses in skeletally mature hypogonadal patients.

/S/ 2/22/95

Linda J. Golden, M.D. Date
Medical Officer

Attachment: Sponsor's submitted draft labeling

cc: Original NDA Arch
HFD-510
HFD-510/SSobel/PCorfman/LGolden/CKish