CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 4-782/S-093

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

FEB 8 1996

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA 4-782
Amendment B-004

SUBMISSION DATE: November 28, 1995

Premarin® Tablets
Conjugated Estrogens
Wyeth-Ayerst Laboratories
Philadelphia, PA

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Clinical Study Report

SYNOPSIS

Reference is made to the approved NDA 4-782 for Premarin® (conjugated estrogens) Tablets. The purpose of this Amendment is to provide a summary report of the clinical study titled "Pilot Study on the Clinical Effects of Δ8,9-dehydroestrone Sulfate in Comparison to Estrone Sulfate". This study was conducted by Dr. Edmund Baracat, Professor and Chair in the Department of Obstetrics and Gynecology at Escola Paulista de Medicine, Sao Paulo, Brazil, evaluating the clinical effects of Δ8,9-dehydroestrone sulfate in postmenopausal women.

This study describes the effects of Δ8,9-dehydroestrone sulfate on vasomotor symptoms, biochemical markers of bone resorption, neuroendocrine markers of estrogen action and serum lipids in postmenopausal women. The doses of Δ8,9-dehydroestrone sulfate (0.125 mg/day) and estrone sulfate (1.45 mg/day) selected for this study are the amounts equivalent to that which would be present in a 2.5 mg Premarin Tablet.

RECOMMENDATION:

The Division of Pharmaceutical Evaluation II has briefly reviewed the information included in Amendment B-004 to NDA 4-782 which was submitted on November 28, 1995. However, due to the fact that this submission is a clinical report that does not include any pharmacokinetic data, HFD-870 believes that no further review is needed for this Amendment. The Division of Pharmaceutical Evaluation II recommends that this submission be directed to Dr. Linda Golden, medical reviewer HFD-510.

/S/ 2/8/96

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by John Hunt. JPH 2/7/96
FT Initialed by John Hunt. 2/8/96

cc: NDA 4-782, HFD-510(Golden, Kish), HFD-427 (M. Chen, Dorantes), Drug, Chron, and Reviewer

ORIGINAL

APR 23 1996

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

Division of Pharmaceutical Evaluation II

NDA 4-782
Amendment to Supplement Serial No. 093

SUBMISSION DATE: June 19, 1995

Premarin Tablets
Conjugated Estrogens
Wyeth-Ayerst Laboratories
Philadelphia, PA

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Labeling Update

CODE: 1S

SYNOPSIS

Premarin (conjugated estrogens) is a natural product derived from pregnant mare's urine. It is comprised of a mixture of sodium estrone sulfate, sodium equilin sulfate and some other conjugated estrogenic substances of the type excreted by pregnant mares.

Reference is made to the approved NDA 4-782 for Premarin Tablets and to the pending supplemental application (Serial No. 093) dated February 15, 1994 for labeling changes. Further reference is made to the FDA letter dated February 22, 1995 which indicated that before this supplement could be approved, a revised version of the labeling incorporating specific language from the "1992 Estrogen Drug Products Labeling Guidance" should be submitted.

Accordingly, the purpose of the Amendment to Supplement Serial No. 093 submitted on June 19, 1995 is to provide a revised version of the labeling based on the "1992 Estrogen Drug Products Class Labeling Guidance". The sponsor noted that upon approval of this submission, the proposed labeling will supersede the following pending supplemental applications.

- Serial No. 096 Providing for lower dosing recommendations for the treatment of vasomotor symptoms under the DOSAGE and ADMINISTRATION section;

The proposed revised draft labeling for Premarin Tablets is included in Attachment I. The template for this draft is based on the "1992 Estrogen Drug Products Class Labeling Guidance". All additions or deletions of text, with subsequent deviations from the guidance text, are indicated by shading or strike-out, respectively. The

sponsor states that deviations from the labeling guidance are, in general, revisions made to provide consistency with the labeling for PREMPRO and PREMPHASE (see Attachment II).

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the Amendment to Supplement No. 093 dated June 19, 1995 for NDA 4-782 for Premarin (conjugated estrogens) Tablets. Due to the fact that i) there is not an established "modified release" definition in the current USP 23, 1995 and ii) that currently the Agency is reviewing the definitions for controlled release, sustained release, extended release, etc., in order to specifically define the various terms, OCPB/DPEII recommends not to include the "modified release formulation" term in Premarin labeling until the definition issue is resolved. Additionally, in order to maintain labeling consistency, it is recommended that a Pharmacokinetics subsection consistent with that of the approved PREMPRO and PREMPHASE products for the 0.625 mg Premarin Tablet be included in the Clinical Pharmacology section of Premarin's labeling but the "modified release" term be excluded.

Additionally, specific pharmacokinetic/bioavailability information for the other strengths of Premarin tablets (0.3, 0.9, 1.25, and 2.5 mg) should be included in the labeling and any study reports supporting such information should be submitted to the agency for review. The sponsor should communicate to the Agency if they do not have *in vivo* pharmacokinetic/bioavailability data for those other strengths for which *in vitro* dissolution data using the "long" dissolution method has shown different dissolution profiles. After the Clinical Pharmacology section of Premarin labeling is reorganized to incorporate the recommended changes, the sponsor should resubmit the package insert for review.

Also, the sponsor should be informed that at the present time the Agency has concerns about the "modified release formulation" descriptor included in PREMPRO and PREMPHASE labelings, but no action will be taken until the "modified release" definition issue is resolved.

Please convey the above Recommendation as appropriate to the sponsor.

/S/ 4/23/96

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by John Hunt. JPH 2/25/96

FT Initialed by John Hunt. 4/23/96

cc: NDA 20-472, HFD-340 (Viswanathan), HFD-510(Golden, Kish), HFD-850 (Lesko), HFD-860 (Malinowski), HFD-870 (M. Chen, Dorantes), HFD-880 (Fleischer), HFD-870/Bott (Drug, Chron, reviewer), and HFD-205 (FOI).

JAN 8 1997

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA 4-782
Amendment Serial No. 093

SUBMISSION DATE: February 21, 1996

Premarin® Tablets
Conjugated Estrogens
Wyeth-Ayerst Laboratories
Philadelphia, PA

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Sponsor's Response

Code: 1S

SYNOPSIS:

Reference is made to the approved NDA 4-782 for Premarin® (conjugated estrogens, USP) Tablets. On February 21, 1996 the sponsor submitted Amendment Serial No. 093 to NDA 4-782 which includes the responses to the four Biopharm Comments outlined in the Agency's letter dated November 7, 1995. Attachment I includes complete information of the sponsor's responses to these Comments.

The reviewer's comments on the sponsor's responses are presented below:

Comment to Response No. 1

Overall, the validation of the method included in report GTR 23559 is appropriate and the analytical method used to determine unconjugated and conjugated $\Delta^{8,9}$-dehydroestrone is acceptable.

Comment to Response No. 2

The provided protein binding information is useful but it is incomplete. Therefore, it is recommended that if additional protein binding data becomes available for Premarin estrogens and their respective sulfates, these data should be submitted to the Agency.

Comment to Responses No. 3 and 4

The sponsor has provided the requested information and their responses to FDA Comments No. 3 and 4 are acceptable

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) acknowledges the submission of the requested information included in Amendment Serial No. 093 to NDA 4-782 for Premarin® Tablets which was submitted on February 21, 1996. The sponsor's responses No. 1, 3, and 4 to the FDA requests for additional information are acceptable. However, the Comment to response No. 2 should be communicated to the sponsor.

Lastly, it should be noted that if a thorough critical review of the potency and bioactivity information and their relationship/contribution to the clinical activity of the $\Delta^{8,9}$ dehydroestrone and 17b-$\Delta^{8,9}$ dehydroestradiol is needed, it is recommended that such information be directed to an Agency's pharmacologist/immunologist specialized in these issues for his/her expert opinion and review.

Please convey the Recommendation as appropriate to the sponsor.

/S/ 1/8/97

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by John P. Hunt. JPH 1/7/97

RD Initialed by John P. Hunt. 1/8/97

cc: NDA 4-782, HFD-580 (VanDerVlugt, Moore), HFD-870 (M. Chen, Dorantes and C. Bott [for Drug])

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 4-782/S-093

BIOEQUIVALENCE REVIEW(S)

OCT 19 1995

NDA 4-782

SUBMISSION DATES: Nov. 30, 1994

Premarin® Tablets
Conjugated Estrogens
Wyeth-Ayerst Laboratories
P.O. Box 8399
Philadelphia, PA 19101

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: NDA Amendment

SYNOPSIS

On November 30, 1994 the sponsor submitted an Amendment to the approved NDA 4-782 for Premarin® (conjugated estrogens, USP) Tablets. Premarin® is a natural product derived from pregnant mare's urine. It is comprised of a mixture of the sodium estrone sulfate and sodium equilin sulfate and some other conjugated estrogenic substances of the type excreted by pregnant mares.

In this Amendment reference is made to a March 1, 1994 Wyeth-Ayerst letter addressed to Dr. Roger Williams and Mr. Douglas Sporn of the FDA. This letter provided the sponsor's comments on the continued regulation of conjugated estrogens drug products by CDER. One of the issues discussed in the letter was the status of Δ8,9-dehydroestrone sulfate as a component in conjugated estrogens. Among other issues, the letter described i) *in vivo* pharmacology data regarding lipid effects and antioxidant activity of Δ8,9-dehydroestrone and ii) pharmacokinetic data regarding Δ8,9-dehydroestrone sulfate and Δ8,9-dehydroestrone following administration of Premarin®.

The purpose of this Amendment was to provide the reports cited in the March 1, 1994 letter. The following reports were included in this submission:

- GTR 25, 554 "Effects of Δ8,9-dehydroestrone and Other Premarin® Components on Lipid Levels in the Rat."
- GTR 25,555 "Effects of Premarin® Components on the Oxidative Modification of LDL *In Vitro*."
- GMR 23,669 "A Comparative Bioavailability Study of Premarin® (0.625 mg) and Estratab® (0.625 mg) in Healthy Postmenopausal Women: Final Report."

Pharmacokinetic study GMR 23,669 (Protocol No. 713-X-108-US) was an open label, single-dose, randomized, two-period crossover study. Its objective was to evaluate the relative bioavailability of 2 x 0.625 mg tablets of Estratab® (esterified estrogens) with respect to that of 2 x 0.625 mg tablets of Premarin® (conjugated estrogens). Twenty-six healthy postmenopausal women were enrolled in the study and 25 women completed the study. Each subject received single oral doses of 1.25 mg (2 x 0.625 mg tablets) of each treatment on two separate occasions under fasting conditions. Venous blood samples were collected at 0, 1.5, 3, 4.5, 6, 7.5, 9,

10.5, 12, 14, 16, 24, 32, 40, and 48 hours and plasma concentrations of the following estrogens were determined: estrone, total estrone, equilin, total equilin, 17β-estradiol, 17β-dihydroequilin, Δ8,9-dehydroestrone, and total Δ8,9-dehydroestrone. Plasma concentrations of the above unconjugated estrogens were determined by and plasma concentrations of the total (conjugated + unconjugated) estrogens were determined by the same method after glusulase hydrolysis. The overall results of this study showed that the 0.625 mg Estratab® and Premarin® tablets are not bioequivalent (90% confidence intervals) with respect to either the rate or extent of absorption for estrone, equilin, total estrone, total equilin, 17β-estradiol, and 17β-dihydroequilin. No statistical comparisons were made for Δ8,9-dehydroestrone between the two treatments.

Peak plasma levels of total Δ8,9-dehydroestrone and the extent of absorption of total Δ8,9-dehydroestrone in the plasma (area under the curve, AUC) were, respectively, approximately half the peak and total levels of total equilin. The firm claims that as there is about six times as much equilin sulfate in Premarin® tablets as there is Δ8,9-dehydroestrone sulfate, this indicates a high relative absorption of Δ8,9-dehydroestrone sulfate. The firm also claims that this disproportionate absorption in favor of Δ8,9-dehydroestrone sulfate was also seen when the results were compared to absorption of estrone sulfate, the other component of conjugated estrogens considered to be of importance.

Comments for Δ8,9-dehydroestrone:

1. The assay method used for this study to determine plasma concentrations of everything except the Δ8,9 components, was previously used and found to be acceptable for the approved Wyeth-Ayerst NDA for the combination Premarin and medroxyprogesterone product. For the Δ8,9 components inadequate assay validation information was provided.

2. Metabolic and potency information for the Δ8,9 components was not provided.

3. Spot checking Cmax and calculated AUC values indicates that they are accurate.

4. The firm stated, "*That peak plasma levels of total Δ8,9-dehydroestrone (i.e., conjugated and unconjugated Δ8,9-dehydroestrone, and its metabolite), and the extent of absorption of total Δ8,9 -dehydroestrone in the plasma (AUC) were, respectively half the peak total levels of total equilin.*" Our calculations indicate total Δ8,9 dehydroestrone (i.e., conjugated and unconjugated Δ8,9-dehydroestrone) Cmax and AUC(infinity) values to be about one third and one half, respectively, of total equilin.

5. Close inspection of unconjugated Δ8,9-dehydroestrone plasma levels indicates the following.

   No. of subjects with no detectable levels = 7 (28%)
   No. of subjects with 1 value (10-12 pg/mL) = 8 (32%)
   No. of subjects with 2-3 values (10-17 pg/mL) = 4 (16%)
   No. of subjects with ≥ 4 values (10-32 pg/mL) = 6 (24%)

   Note: The assay's minimum quantifiable concentration is pg/mL.

6. Close inspection of total Δ8,9-dehydroestrone plasma levels indicates all subjects had detectable levels/profiles.

   Note: The assay's minimum quantifiable concentration is pg/mL.

7. It is noted that the determined plasma concentrations represent both bound and unbound levels for different measured components. No protein binding data were provided for the conjugated and unconjugated Δ8,9 components. This needs to be considered in interpreting the provided information.

RECOMMENDATION:

The Division of Pharmaceutical Evaluation II has reviewed the final report for study GMR 23,669 included in the Amendment to NDA 4-782 which was submitted on November 30, 1994 for Premarin® (conjugated estrogens). During the reviewing process, it was found that the information included in the pharmacokinetic report for study GMR 23,669 was incomplete. Therefore, before a final recommendation can be given for the above study, the sponsor needs to provide the following additional information i) assay validation data for the analytical method(s) used to quantify unconjugated Δ8,9-dehydroestrone and total Δ8,9-dehydroestrone, ii) protein binding information for different plasma proteins (i.e., SHBG, α_1-acid glycoproteins, albumin, etc.) for 17α-dihydroequilin, 17β-dihydroequilin, Δ8,9-dehydroestrone, and their respective sulfates, iii) because the study data indicate disproportionately large AUC and Cmax values to total Δ8,9-dehydroestrone, metabolism, and potency data for this compound and its metabolites are needed in order to assess the significance of the limited data (include full reports), and iv) hard copies for some of the references included in pages 53 to 55 (i.e., 1 to 20 and 22 to 26).

With respect to the pharmacology reports GTR 25,554 and GTR 25,555 included in this Amendment, Division of Pharmaceutical Evaluation II recommends that these reports be directed to the reviewing Pharmacologist of HFD-510 for review. Additionally, if HFD-510 has received for review any *in vitro* and/or animal studies in which the potency (receptor binding affinity and biological activity) of the estrogenic components of Premarin® was studied, this Division would like to know if the information included in those studies has been thoroughly evaluated by HFD-510.

Please request the additional information needed for the completion of this review.

/S/

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by John Hunt. JPH 10/16/95
FT Initialed by John Hunt. 10/19/95

cc: NDA 4-782, HFD-510, HFD-427 (M. Chen, Dorantes), Drug, Chron, F, and HFD-19 (FOI)

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the Amendment to Supplement No. 093 dated June 19, 1995 for NDA 4-782 for Premarin (conjugated estrogens) Tablets. Due to the fact that I) there is not an established "modified release" definition in the current USP 23, 1995 and II) that currently the Agency is reviewing the definitions for controlled release, sustained release, extended release, etc., in order to specifically define the various terms, OCPB/DPEII recommends not to include the "modified release formulation" term in Premarin labeling until the definition issue is resolved. Additionally, in order to maintain labeling consistency, it is recommended that a Pharmacokinetics subsection consistent with that of the approved PREMPRO and PREMPHASE products for the 0.625 mg Premarin Tablet be included in the Clinical Pharmacology section of Premarin's labeling but the "modified release" term be excluded.

Additionally, specific pharmacokinetic/bioavailability information for the other strengths of Premarin tablets (0.3, 0.9, 1.25, and 2.5 mg) should be included in the labeling and any study reports supporting such information should be submitted to the agency for review. The sponsor should communicate to the Agency if they do not have *in vivo* pharmacokinetic/bioavailability data for those other strengths for which *in vitro* dissolution data using the "long" dissolution method has shown different dissolution profiles. After the Clinical Pharmacology section of Premarin labeling is reorganized to incorporate the recommended changes, the sponsor should resubmit the package insert for review.

Also, the sponsor should be informed that at the present time the Agency has concerns about the "modified release formulation" descriptor included in PREMPRO and PREMPHASE labelings, but no action will be taken until the "modified release" definition issue is resolved.

Please convey the above Recommendation as appropriate to the sponsor.

Cleared for Faxing: /S/ 5/10/96

Solomon Sobel, M.D.
Division Director

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 4-782/S-093

ADMINISTRATIVE DOCUMENTS

CSO Review of Revised Draft Labeling

NDA: 4-782/S-093 Premarin (conjugated estrogen) Tablets
Original Submission: February 15, 1994
First Revision Submission: June 19, 1995
Final Revision Submission: March 2, 1998

Background:

The original efficacy submission provided for a revision of the **DOSAGE AND ADMINISTRATION** section for the indicated treatment of female hypogonadism to reduce the recommended dosage.

The application was reviewed and found approvable on February 22, 1995. A provision of the approval was the updating of the Premarin Labeling to the August 1992 draft Labeling Guidance for Estrogen Drug Products and to include several other revisions specific to this drug product.

The sponsor submitted revised draft labeling June 19, 1995, which contained most of the changes requested. The labeling was reviewed by the Medical Officer, Chemist and Clinical Pharmacologist.

The Medical Officer review was completed January 4, 1996. The Clinical Pharmacologist also completed a review however, the statement regarding the release characteristics the sponsor was claiming was originally overlooked and a second review period to examine this claim was required.

In the interim between the completion of the Medical Officer's review and the second review of the Clinical Pharmacologist the sponsor was contacted by the Division and informed of the additional changes to the submitted draft requested by the Medical Officer.

the sponsor submitted a second draft with some of these changes implemented. However, the Clinical Pharmacologist, after numerous consultations with various members of that Division requested that the modified release characteristics claimed by the sponsor for this drug product be removed because this descriptor was not recognized by the USP.

The sponsor submitted further revised draft labeling incorporating the changes from draft number 2 and deletion of the modified release descriptor on March 2, 1998.

This review is based on the March 1998, draft and the January 4, 1996, Medical Officer's review (attached as reference).

Only changes that were requested by, not made by, the sponsor are discussed all other areas are acceptable as submitted.

Prescribing Information

CLINICAL PHARMACOLOGY section

The Medical Officer requested that the ratio of total cholesterol/HDL be deleted from this table. This change has now been made.

INDICATIONS AND USAGE section

6. Prevention and Treatment of Osteoporosis subsection

The Medical Officer requested that be deleted from this subsection title. This change has not been made.

WARNINGS section

1. Induction of Malignant Neoplasm subsection

subheading

The Medical Officer requested the following language be utilized in the second paragraph:

The sponsor has incorporated this language into paragraph two such that it now reads:

2. Gallbladder Disease subsection

The Medical Officer requested this subsection read as follows:

This change has been made by the sponsor.

PRECAUTIONS section

The Medical Officer requested that the first paragraph be underlined and in bold. The sponsor has underlined the first paragraph but has left it unbolded.

The Medical Officer also requested that clinical data be submitted to support the addition of hypocalcemia (subheading number 10). This data has not bee submitted however, the subheading remains present and reads:

DOSAGE AND ADMINISTRATION section

Subsection **1.**

The sponsor was requested to correct the spelling of vulvar in this section. The sponsor has complied with this request. Additionally, the sponsor was requested to delete the second and third sentence from paragraph 2. The sponsor has also complied with this request.

Subsection **2.**

The sponsor was requested to reverse the order of paragraphs 2 and 3. The sponsor has complied with this request.

Subsection **5.**

The sponsor was requested to delete the words from the phrase This has not been deleted.

Information for the Patient

USES OF ESTROGEN section

To Reduce Moderate to Severe Menopausal Symptoms subsection

The sponsor was requested to revise the second paragraph to insert the following test as the third, fourth and fifth sentences:

The sponsor has not made this revision.

RISKS OF TAKING ESTROGENS section

The sponsor has revised this sections title from The sponsor was requested to return the heading to it's original wording. This has not been done.

4. Inflammation of the pancreas subsection

The sponsor was requested to revise the test of this subsection from:

To:

This revision has not been made.

OTHER INFORMATION section

The sponsor was requested to revise the second paragraph of the second sentence as follows:

The sponsor has incorporated this wording into a second paragraph which now reads:

/S/

Christina Kish

DF

FEB - 1 1996

NDA 4-782/S-093

CSO REVIEW OF FPL

NDA 4-782 SUPPL-93

FPL SUBMISSION DATE: NA

SUPPLEMENT APPROVABLE DATE: 2/22/95

DATE REVISED DRAFT WAS SUBMITTED: 6/19/95

LABELING PIECES REVIEWED:
Both Physician and Patient Package inserts in conjunction with the estrogen labeling guidance (8/92), and the approved draft labeling for NDA 20-527.

REVIEW & COMMENTS:
Overall comments: The approvable letter (issued 2/22/95) for this supplement outlined ten pages of required text changes to be made throughout the physician and patient package inserts. The revised labeling which was submitted to the Agency in response to the approvable letter is exactly the same as the estrogen labeling guidance with a few exceptions. If the approvable letter requested specific wording, and the guidance had different wording, the wording from the approvable letter was used. In every case, the requirements laid out in the approvable letter were followed. Other changes were minor editorial changes (e.g., guidance says should ideally... sponsor writes ideally should etc.). Finally, the sponsor has also added a section "Information Regarding Lipid Effects" while not in the approvable letter or guidance document, it was approved in NDA 20-527.

Specific Comments:

Physician Package Insert:
The boxed warning has been reinstated in its entirety exactly as it is found in the guidance document, and as requested in the letter of February 22, 1995 (AE letter).

The DESCRIPTION section reflects the changes requested in the AE letter, however the reviewing chemist will be asked to review this section again. It was noted in this review that an ingredient in the 0.9 mg tablet (polysorbate 20) has been inadvertently omitted. Note: Dr. Moore telephoned Ms. Joan Barton at Wyeth-Ayerst concerning the deletion of this ingredient.

The CLINICAL PHARMACOLOGY section reflects for the most part the guidance document exactly. Changes include minor editorial changes which do not change meaning, a deletion of the GI tract from the paragraph describing the absorption of estrogens (Paragraph 5 in revised draft). However there are also some very large changes as follows:

Paragraph 4 is a new paragraph not found in the guidance or requested in the AE letter. This paragraph outlines the modified release characteristic of Premarin.

Paragraph 8 is the beginning of a new subsection "Information Regarding Lipid Effects" and is very similar to the approved draft labeling for NDA 20-527. The text reads:

> "The results of a clinical trial conducted in a 97% Caucasian population at low risk for cardiovascular disease show that Premarin significantly increases HDL-C and HDL_2-C subfraction and significantly decreases LDL-C.
>
> The following table summarizes mean percent changes from baseline lipid parameter values after 1 year of treatment with Premarin."

Following this Paragraph is a lipid table in which various lipid parameters and their values from Premarin 0.625 mg alone is given. The only new value on this table is Total Cholesterol/HDL ration which is given as -10.8. All other parameters and values are identical to the table approved in the draft labeling for NDA 20-527.

The INDICATIONS AND USAGE section is like the guidance except that treatment of abnormal uterine bleeding due to hormonal imbalance is left out (lined out). and Prevention of osteoporosis is now Prevention and treatment of osteoporosis.

CONTRAINDICATIONS section also reflects the guidance document, with an additional contraindication which reads "Premarin Tablets should not be used in patients hypersensitive to their ingredients."

The WARNINGS section reflects the guidance document unless there was specific language requested in the AE letter, in which case the language from the AE letter was used. The second paragraph is new, and reflects the PEPI trial data, the language used is the same as that used in the approved draft labeling of NDA 20-527 . In the "Gallbladder disease" subsection, the wording surgically confirmed is used instead of requiring surgery.

The PRECAUTIONS section also reflects the guidance document, the second paragraph is altered to reflect the changes requested in the AE letter. The Cardiovascular Risk subsection is there in toto, however it is not underlined. Paragraph 10 has several changes which should be reviewed by the medical officer, but overall reflect both the guidance and the AE letter. A section on Uterine fibroids has been added as requested by the AE letter. Also added is a subsection on hypocalcemia which reads:

The ADVERSE REACTIONS section reflects the guidance document, and includes all requests from the AE letter, it also includes Pancreatitis under the gastrointestinal subsection.

OVERDOSAGE is also like the guidance document.

DOSAGE AND ADMINISTRATION follows the guidance document, and incorporates the requests made in the AE letter including deletion of atrophic urethritis, and the inclusion of the pharmacodynamic text regarding delayed puberty. It will be necessary for both the medical officer and the reviewing chemist to review this section however to be sure that all appropriate changes have been made.

The HOW SUPPLIED section should be reviewed by the reviewing chemist prior to any letter to the sponsor.

Patient Package Insert:

INTRODUCTION is the same as the guidance document and reflects the changes requested in the AE letter.

BOXED WARNING also reflects the guidance document as requested in the AE letter.

The USES OF ESTROGEN SECTION reflects the guidance document and the AE letter except for paragraph four which while similar to the guidance document has a very different "spin" and should be reviewed by the medical officer.

WHO SHOULD NOT USE ESTROGENS reflects the guidance document but substitutes the word where the guidance document states

DANGERS OF ESTROGENS also reflects the guidance document, again the word is put in place of including the heading which now reads The wording for breast exams as requested in the AE letter has been inserted, and a new subsection has also been added which reads:

SIDE EFFECTS reflects the guidance document. —

REDUCING RISK OF ESTROGEN USE reflects the guidance document.

OTHER INFORMATION is like the guidance document but the second paragraph does include wording regarding lipid effects that should be reviewed by the medical officer since the words used were under discussion during the review of NDA 20-527 and NDA 20-303.

THE HOW SUPPLIED section of this label should be reviewed by the reviewing chemist prior to approval of this draft labeling.

/S/ 2/1/96

Note: Dr.'s Golden and Moore have reviewed their recommended sections, See MOR and coverletter of June 19, 1995.

cc: Arch. NDA
HFD-510
HFD-510/CKish/12.18.95/n4782.lr93

Concurrences:SMoore 1.17.96/LGolden 1.2.96/LRarick 1.17.96/EGalliers 1.31.96/PCorfman 1.4.96

Exclusivity Summary Form

EXCLUSIVITY SUMMARY FOR NDA # _4-782_____ SUPPL #__093____

Trade Name: _Premarin_____ Generic Name: _Conjugated Estrogens (0.3, 0.625, 0.9, 1.25, and 2.5 mg) Tablets_____

Applicant Name: Wyeth-Ayerst_____ HFD # _580_____

Approval Date If Known:___September 8, 1998_____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. **An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.**

   a) **Is it an original NDA?**

   YES/___/ NO /_X__/

   b) **Is it an effectiveness supplement?**

   YES /_X__/ NO /___/

   If yes, what type? (SE1, SE2, etc.) __SE2_____

   c) **Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")**

   YES /___/ NO /_X__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) **Did the applicant request exclusivity?**

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. **Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)**

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. **Is this drug product or indication a DESI upgrade?**

YES /_X__/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.
(Answer either #1 or #2 as appropriate)

1. **Single active ingredient product.**

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

2. **Combination product.**

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

(1) **If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.**

YES /___/ NO /___/

If yes, explain:

(2) **If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?**

YES /___/ NO /___/

If yes, explain: As submitted in the supplemental application

(c) **If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:**

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. **In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.**

a) **For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")**

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) **For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?**

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

(c) **If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):**

_____ _____

_____ _____

4. **To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.**

a) **For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?**

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

Signature:

Date:

Title:

Signature of Office/Division Director

Signature: /S/

Date: 11-6-98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

BLA #_NDA 4-782_____ Supplement # __SE2-093_____Circle one: SE1 [SE2] SE3 SE4 SE6

HFD-580__ Trade and generic names/dosage form: _Premarin® (conjugated estrogens) Tablets__Action: [AP] AE NA

Applicant _Wyeth-Ayerst Research_____ Therapeutic Class____3S_____

1. Indication(s) previously approved _ Treatment of moderate to severe vasomotor symptoms associated with the menopause; Treatment of vulval and vaginal atrophy; treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure, Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease, Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only, and prevention of osteoporosis._____

Pediatric information in labeling of approved indication(s) is adequate _X_ inadequate __

Proposed indication in this application___none_____

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? _X__Yes (Continue with questions) ___ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___Neonates (Birth-1 month) __ Infants (1month-2yrs) __Children (2-12yrs) _X__ Adolescents (12-16 yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

_X__ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

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

___ (1) Studies are ongoing.
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. 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.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes _X__ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from _Medical review_____ (e.g., medical review, medical officer, team leader)

/S/
ature Of Preparer And Title

12/8/98
Date

CC: ORIG NDA/BLA # NDA 4-782___
HFD-580__/DIV FILE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 4-782/S-093

CORRESPONDENCE

NDA 4-782

NOV 28 1997

Wyeth-Ayerst Research
Attention: Mr. Justin R. Victoria
Vice President
U.S. Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Victoria:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Premarin NDA 4-782.

We further refer to your February 25, 1997, submission providing for your General Technical Report (GTR) 29548 entitled, "A Steady-State Bioavailability Study with Premarin (2 x 0.625 mg) in healthy Post-Menopausal Women – Final Report."

We have completed our review of the your submission and have the following request for further information:

> The Quality Control (QC) sample results for the analysis of total 17β-estradiol and total 17β-$\Delta^{8,9}$ dehydroestradiol suggest that these estrogens may be overestimated in this study. Please provide an explanation for the upward bias seen in the QC samples for total 17β-estradiol and total 17β-$\Delta^{8,9}$ dehydroestradiol.

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

Sincerely,

/S/ 1/26/97

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

cc:
Original NDA 4-782
HFD-580/Div. Files
HFD-580/CSO/D.Moore
HFD-580/LRarick/HJolson/Tvan der Vlugt/Dorantes
HFD-510/MFossler

Drafted by: dm/October 24, 1997/n4782ir.snc

Concurrences:
LPauls 10.27.97/MFossler 10.28.97/ADorantes 11.12.97/Tvan der Vlugt 11.13.97
HJolson 11.13.97/LRarick 11.24.97

INFORMATION REQUEST (IR)

11/25/97

FEB 28 1997

NDA 4-782/S-093

Wyeth-Ayerst
Attention: Mr. Justin R. Victoria
Vice President, Project Management
P.O. Box 8299
Philadelphia, PA 19101

Dear Mr. Victoria:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Premarin® tablets.

We also refer to your submission dated November 30, 1994, in which you provided Protocol 713-X-108-US, entitled "A Comparative Bioavailability Study of Premarin® (0.625 mg) and Estratab® (0.625 mg) in Healthy Postmenopausal Women". We further refer to your submissions dated February 21, and June 17, 1996, in which you provided analytic methods and pharmacokinetic data for Protocol CF-DHE-001 BR, entitled "Pilot Study on the Clinical Effects of Delta 8,9-dehydroestrone Sulfate in Comparison to Estrone Sulfate". We also refer to your August 1, 1996, submission, which provided additional pharmacokinetic and analytic methods information.

We have completed the analytical portion of the Clinical and Pharmacology and Biopharmaceutics section of your submission and have identified the following deficiencies:

1. Dates of specific method validations and dates when postmenopausal plasma samples were assayed are sometimes not clear for GMR-23669 (Comparative study of Premarin® and Estratab®), and the pharmacokinetic samples assayed due to protocol CF-DHE-001BR (Pilot study on the clinical effects of $\Delta^{8,9}$-dehydroestrone sulfate alone or in combination with estrone sulfate). For the plasma sample assays of estrone, equilin, $\Delta^{8,9}$-dehydroestrone, 17β-estradiol, 17β-dihydroequilin, and 17β-$\Delta^{8,9}$-dehydroestradiol, unconjugated and total, as applicable, associated with these studies, please identify:

   a. the specific methods validation report(s) (General Technical Report, GTR) upon which the assay of each estrogen component was based;
   b. the actual dates when each of the methods was validated;
   c. if additional methods validation was conducted after assay of the plasma samples, these reports should be identified, along with the specific estrogens and study(ies) to which the validation applies; and
   d. the dates of assay of each of the above estrogens from both studies.

2. **Synthetic 17β-$\Delta^{8,9}$-dehydroestradiol**: Please provide data other than mass spectral analysis to confirm the structural identity of the synthetic 17β-$\Delta^{8,9}$-dehydroestradiol

reference material; NMR and other relevant structural data, and purity information for the synthetic material.

3. **Identification of 17β-$\Delta^{8,9}$-dehydroestradiol in plasma of women receiving Premarin®:** Figure 3 in GTR-26160 and Figure 1 in GTR-26453 present mass chromatograms of plasma extracts from women receiving Premarin® identifying 17β-dihydroequilin and an unknown peak which co-elutes with synthetic 17β-$\Delta^{8,9}$-dehydroestradiol. Data before and after spiking with the synthetic estrogen are shown in Panels A and B, respectively. Panel A appears to be the same data but Panel B is obviously different data for the two reports. In addition, the peak identified as 17β-dihydroequilin is different for the two reports. Please provide an explanation for this apparent inconsistency in the presentation of the data.

4. **Plasma 17β-$\Delta^{8,9}$-dehydroestradiol:** Plasma concentrations in postmenopausal women of 17β-$\Delta^{8,9}$-dehydroestradiol were reported in Wyeth-Ayerst GTR-27274 and GTR-27778 following dosing of $\Delta^{8,9}$-dehydroestrone sulfate in the Brazilian study (Protocol CF-DHE-001BR). It appears that plasma concentrations of the claimed 17β-$\Delta^{8,9}$-dehydroestradiol were high enough to obtain full mass spectra and product ion scans, etc. Please provide additional available conformational data for the structural identification of the 17β-$\Delta^{8,9}$-dehydroestradiol present in plasma of these subjects.

5. The mass spectral ion fragment, $(M-64)^{\cdot}$, is rather unique, presumably requiring a molecular fragment loss and rearrangement. Why doesn't the same loss occur in all estrogens analyzed? Do you have references to similar mass spectral losses for steroids? Were any product ion experiments performed on this ion fragment?

6. The observation that equilin can be converted to $\Delta^{8,9}$-dehydroestrone (GTR-23559) is of concern. Is this conversion due to sample processing or is $\Delta^{8,9}$-dehydroestrone a possible metabolic product of equilin? Please provide available data concerning conversion of equilin to $\Delta^{8,9}$-dehydroestrone including the *in vivo* metabolism of equilin in humans or animals.

7. It is unclear why GMR-23669 did not contain data for total 17β-dihydroequilin and 17β-estradiol plasma concentrations and pharmacokinetic summaries for these two compounds since validation for quantification of total plasma concentration of these compounds is contained in GTR-20538. In Wyeth-Ayerst GTR-26460 dated September 1995, you refer to Wyeth-Ayerst GTR-20538 and GTR-23307 for analytical methodology used to determine unconjugated dihydroequilin and 17β-estradiol plasma concentrations for the comparative bioavailability study. When were the analytical performance standards reported in Wyeth-Ayerst GTR-26460 performed? Was it before or after the subjects plasma samples reported in Wyeth-Ayerst GMR-23669 were analyzed? Do the estrogen plasma concentrations reported in Wyeth-Ayerst GTR-26460 represent recalculations of plasma data previously obtained?

8. The data presented in GTR-27857 and GTR-27104 indicate that isotopic content is highly variable in the deuterated $\Delta^{8,9}$-dehydroestrone and 17β-$\Delta^{8,9}$-dehydroestradiol internal standards. Theoretical calculations indicate this could results in nonlinear calibration curves which could result in poor accuracy for the measurements, especially at low concentrations. Please provide the raw area ratios data used to construct the calibration curves for these two compounds.

9. Please provide copies of three general technical reports referenced in GTR-26160 as follows:

   a. GTR-22904:,Chandrasekaran, A. Species comparison of the *in vitro* metabolism of $\Delta^{8,9}$-dehydroestrone by liver microsomes (1995);
   b. GTR-21786: Chandrasekaran, A.J., Jacobs, N., Osman, M. Metabolism of $\Delta^{8,9}$-dehydroestrone in female beagle dogs (1993); and
   c. GTR-22274: Chandrasekaran, A. Biliary metabolite patterns of $\Delta^{8,9}$-dehydroestrone (AY-26364) in rats (1995).

We would appreciate your prompt written response so that we can continue our evaluation of your Citizen's Petition.

If you have any questions, please contact Diane Moore, Consumer Safety Officer, at (301) 827-4260.

Sincerely,

/S/

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

cc:
Original NDA N 4-78
HFD-580/Div. Files
HFD-580/CSO/D.Moore
HFD-580/LRarick/HJolson/T van der Vlugt
HFD-870/JStrong/ADorantes
HFD-604/WAdams

Drafted by: dm/January 29, 1997/n4782bs.093

2/25/97

Concurrence:
LPauls 02.20.97/ADorantes 02.20.97/T van der Vlugt, HJolson, LRarick 02.21.97
WAdams 02.24.97/JStrong 02.25.97

INFORMATION REQUEST (IR)

NDA 4-782/S-093

NOV - 7 1995

Wyeth-Ayerst Laboratories
Attention: Ms. Joan E. Barton
Manager, Marketed Products
Drug Regulatory Affairs
P.O. Box 8299
PHILADELPHIA PA 19101-1245

Dear Ms. Barton:

Please refer to your February 15, 1994 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Premarin (conjugated estrogens) Tablets.

We also refer to your November 30, 1994, submission, which provides reports cited in your March 1, 1994, letter.

We have completed review of study number GMR 23,669 and have the following comments and requests for information:

1. Please provide assay validation data for the analytical method(s) used to quantify unconjugated Δ8,9-dehydroestrone and total Δ8,9-dehydroestrone.

2. Please provide protein binding information for different plasma proteins (i.e., SHBG, α_1-acid glycoproteins, albumin, etc.) for 17α-dihydroequilin, 17β-dihydroequilin, Δ8,9-dehydroestrone and their respective sulfates.

3. Because the study data indicate disproportionately large AUC and Cmax values to total Δ8,9-dehydroestrone, metabolism, and potency data for this compound and its metabolites are needed in order to assess the significance of the limited data, please include full study reports.

4. Please submit hard copies for some of the references included in pages 53 to 55 (i.e., 1 to 20, and 22 to 26).

Should you have any questions, please contact Ms. Christina Kish (301) 443-3510.

Sincerely yours,

/S/

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

cc:
Orig NDA
HFD-510
HFD-870/ADorantes/JHunt
HFD-510/CKish/10.23.95/n4782.ir
concurrences:ADorantes 10.23.95/JHunt 10.23.95/EGalliers 11.3.95

INFORMATION REQUEST (IR)

WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

ORIGINAL

NDA SUPP AMEND
SE2-093 IL

NDA No. 04-782/S-093
Premarin® Tablets

Concurs. Literature included support the addition of #10. Hypocalcemia under the Precautions section. J.L.Iezzoni 8/3/98

July 24, 1998

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Document Control Room 17B-20
Food and Drug Administration (HFD-580)
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Rarick:

Reference is made to our approved New Drug Application No. 04-782 for Premarin, conjugated estrogens, Tablets. Further reference is made to pending supplemental application NDA No. 04-782/S-093, submitted on March 2, 1998, that provides for incorporation of the 1992 Estrogen Drug Products Labeling Guidance text into Premarin labeling.

Reference is also made to a June 16, 1998 telephone conversation between Ms. Diane Moore, Project Manager, Division of Reproductive and Urologic Drug Products and Mr. Robert Quinty of Wyeth-Ayerst during which the following Precautions section of the draft Premarin label was discussed:

Precautions

A General

10. *Hypocalcemia*. "Estrogens should be used with caution in individuals with metabolic bone disease associated with severe hypocalcemia."

During this call, the Agency requested that additional information be provided to support this section of the draft Premarin label.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 27 1998
HFD-580

The purpose of this submission is to provide the Agency with the requested supportive information for the above-proposed wording. The risk of hypocalcemia exists in certain unusual medical conditions in patients being treated with estrogen. This can lead to serious consequences. Provided herewith are four reports from the literature that support the inclusion of the draft Premarin labeling that estrogens should be used with caution in those individuals. A copy of these four reports are provided in Attachment 1.

We trust that you will find this information satisfactory and will approve pending supplemental application S-093 at your earliest convenience. Should you have any questions, please call the undersigned at (610) 902-3772, or Mr. Robert Quinty at (610) 902-3789.

Sincerely,
WYETH-AYERST LABORATORIES

Jennifer W. Phillips, Pharm.D., Director
Women's Health Care Products
U.S. Regulatory Affairs

:rhq:\s093
c.c.: Mrs. Diane Moore, Project Manager, DRUDP, FDA

WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corp.

U.S. REGULATORY AFFAIRS

ORIGINAL

AJ 3/20/98

not filed DTC 9/3/98

NDA SUPP AMEND SE2-093 BL

NDA No. 04-782/S-093
Premarin® Tablets

REVIEWS COMPLETED
CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS 9/3/98 DATE

March 2, 1998

CENTER FOR DRUGS
REC'D
MAR - 3 1998
HFD-580
EVALUATION AND RESEARCH

9/3/98

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Document Control Room 17B-20
Food and Drug Administration (HFD-580)
5600 Fishers Lane
Rockville, MD 20857

Noted LCR 8/19/98

Noted DTC 3/20/98

Dear Dr. Rarick:

Reference is made to our approved New Drug Application No. 04-782 for Premarin®, conjugated estrogens, USP, Tablets.

Further reference is made to pending supplemental application S-093 submitted on February 15, 1994 and amended on June 19, 1995, April 30, 1996 and October 10, 1996 providing for draft labeling to incorporate changes to the Description section to provide the description of estrogen components found in Premarin, text consistent with the 1992 Estrogen Drug Products Labeling Guidance (EDPLG) and a description of the modified release characteristics in the Clinical Pharmacology section, among other changes.

Finally reference is made to a May 13, 1996 facsimile transmission (Appendix A) of a May 10, 1996 recommendation from Dr. Solomon Sobel, Director, Division of Metabolism and Endocrine Drug Products (DMEDP), FDA and several telephone conversations between representatives of DMEDP and Ms. Joan Barton, Wyeth-Ayerst in which Wyeth-Ayerst was requested to remove the "modified release formulation" term from S-093 in order that the Agency would approve labeling for Premarin Tablets that reflects the 1992 Estrogen Drug Products Labeling Guidance.

The purpose of this communication is to amend pending supplemental application S-093 to delete the specific language regarding modified release in the draft Premarin labeling. It is the intention of Wyeth-Ayerst to file a new supplemental application providing for a description of the modified release formulation at a later date. In support of this amendment provided herewith are four copies of the draft labeling page where reference to the modified release formulation of conjugated estrogens has been deleted.

We trust that you will find this labeling satisfactory and will approve supplemental application S-093 at your earliest convenience. Should you have any questions regarding this information, please contact the undersigned at (610) 902-3740 or Mr. Robert Quinty at (610) 902-3789.

Sincerely,
WYETH-AYERST LABORATORIES

Joseph S Sonk, Ph.D., Senior Director
Women's Health Care
U.S. Regulatory Affairs

c.c.: Ms. Christina Kish, Project Manager, DRUDP, FDA
Mrs. Diane Moore, Project Manager, DRUDP, FDA
:rhq:s093