CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-417

CHEMISTRY REVIEW(S)

NDA 21-417

Premarin®
(conjugated estrogens tablets)

Wyeth-Ayerst Laboratories

Sarah C. Pope, Ph.D.
Division of Metabolism and Endocrine Drug Products
(HFD-510)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-417

2. REVIEW #: 2

3. REVIEW DATE: 21-APR-2003

4. REVIEWER: Sarah C. Pope, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	17-DEC-2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	15-JAN-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Wyeth-Ayerst Laboratories
Address:	P.O. Box 8299 Philadelphia, PA 19101-8299
Representative:	N/A
Telephone:	484-865-3743

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Premarin®
b) Non-Proprietary Name (USAN):conjugated estrogens tablets
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 6
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Estrogens, prevention of osteoporosis

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 0.3 mg, 0.45 mg CE

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
__X___SPOTS product – Form Previously Submitted

_____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

a. Conjugated estrogens (CE): see USP 26

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	3	Adequate	03-JUL-2001	Reviewed by Dr. D. Lin
[redacted]	III	[redacted]	[redacted]	3	Adequate	22-MAY-2002	Reviewed by Dr. L. Rocca
[redacted]	III	[redacted]	[redacted]	3	Adequate	27-SEP-2000	Reviewed by Dr. R. Lostritto

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III	3	Adequate	9-FEB-2001	Reviewed by Dr. D. Klein
III	3	Adequate	28-SEP-2000	Reviewed by Dr. D. Klein
III	3	Adequate	14-FEB-2003	Reviewed by Dr. J. Salemme
III	3	Adequate	31-MAR-2001	Reviewed by Dr. D. Lin
III	3	Adequate	02-MAR-2000	Reviewed by Dr. D. Christodoulou
III	3	Adequate	03-AUG-2001	Reviewed by Dr. S. Peri
III	3	Adequate	09-SEPT-2001	Reviewed by Dr. D. Klein
III	3	Adequate	20-APR-2000	Reviewed by Dr. S. Markovsky

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Original NDA	NDA 4-782	Approved NDA for Premarin Tablets, the core tablet for the Prempro drug product
Patent	5,210,081	Drug substance, drug product formulation, method of use. Expiration date: 26-Feb-2012. Patent owner: Wyeth-Ayerst Laboratories

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	08-MAY-2003	R. Woods
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Methods previously validated for approved strengths		

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OPDRA	N/A		
EA	Categorical exclusion granted		David T. Lin, Ph.D. (see Chemistry Review #1)
Microbiology	N/A		

The Chemistry Review for NDA 21-417

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing and controls standpoint, this NDA may be **Approved.**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

Premarin® is an solid oral tablet, and the 0.625 mg dosage strength is currently approved for the prevention of post-menopausal osteoporosis. This NDA proposes the addition of two new Premarin dosage strengths, 0.3 mg CE and 0.45 mg CE, also for the prevention of post-menopausal osteoporosis. The 0.3 mg dosage strength is a green-colored, oval, biconvex sugar-coated tablet. The 0.45 mg dosage strength is a blue-colored, biconvex, sugar-coated tablet. Currently, the 0.3 mg dosage strength tablet is approved for the treatment of vulvar and vaginal atrophy.

The Premarin tablet consists of a core tablet containing Conjugated Estrogens, USP. This core is

The drug product is co-manufactured at the Ayerst Laboratories facility in Rouses Point, NY and the Wyeth Pharmaceuticals facility in Guayama, Puerto Rico. Acceptable specifications have been provided to ensure product quality at release.

Once released, the drug product will be packaged in one of configurations:

(100 count) bottles with The bottles will be the marketed packaging configuration. The relevant DMFs for have been reviewed and determined to be adequate for this drug product.

Based on the stability data provided in the first review cycle for this NDA, a 24-month expiry has been granted for storage at 25 °C/60% RH (controlled room temperature). No additional data have been provided for the approved 0.3 mg dosage strength tablet, and therefore the expiry remains at 36 months when stored at controlled room temperature.

This review covers the Sponsor's complete response submitted to the Agency on 15-JAN-2003. Further information regarding materials reviewed during the first review cycle can be located in Chemistry Review #1 (by Dr. David Lin, 4-OCT-2002).

Drug Substance:
The conjugated estrogens (CE) drug substance is a mixture of conjugated estrogens derived from teh urine of pregnant mares. All of the pertinent CMC information is cross-referenced to NDA 4-782 (Premarin Tablets).

B. Description of How the Drug Product is Intended to be Used

Premarin is administered as a single tablet, once daily, for the prevention of bone loss in postmenopausal women with intact uteri.

The 0.45 mg drug product expiry is 24 months when stored at 20-25 °C (controlled room temperature). The 0.3 mg dosage strength expiry is currently 36 months at the same storage conditions.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC standpoint, this NDA may be Approved. This recommendation is based on the satisfactory resolution of the previous cGMP non-compliance of the Ayerst Rouses Point facility. As stipulated in the Agency's approvable letter issued on 18-OCT-2002, all sites listed in this NDA must be in current GMP compliance. As of 08-MAY-2003, this NDA has been given an overall acceptable recommendation from the Office of Compliance.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: YYang/SPope/20-APR-2003
ChemistryTeamLeaderName/Date: DLin/20-APR-2003
ProjectManagerName/Date: KJohnson/20-APR-2003

C. CC Block

HFD-510/Division File/NDA 21-417
HFD-580/SPope/DLin
HFD-510/KJohnson

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/s/

Sarah Pope
5/12/03 04:46:01 PM
CHEMIST

David T. Lin
5/12/03 05:46:23 PM
CHEMIST
I concur.

CHEMISTRY REVIEW

NDA 21-417

Premarin®
(conjugated estrogens tablets)

Wyeth-Ayerst Laboratories

David T. Lin, Ph.D.
Division of Metabolism and Endocrine Drug Products
(HFD-510)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-417

2. REVIEW #: 1

3. REVIEW DATE: 04-OCT-2002

4. REVIEWER: David T. Lin, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
none	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	17-DEC-2001

7. NAME & ADDRESS OF APPLICANT:

Name:	Wyeth-Ayerst Laboratories
Address:	P.O. Box 8299 Philadelphia, PA 19101-8299
Representative:	N/A
Telephone:	484-865-3743

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Premarin®
b) Non-Proprietary Name (USAN): conjugated estrogens tablets
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 6
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Estrogens, treatment of osteoporosis

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 0.3, 0.45 mg (0.3 mg approved for vulvar and vaginal atrophy)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note21]:

___x__SPOTS product – Form Completed

_____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Conjugated estrogens (CE): see USP 25

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III			3	Adequate	7/3/01	Reviewed by Dr. D. Lin
	III				Adequate	12/17/99	Reviewed by Dr. J. Boal
	III			3	Adequate	9/27/00	Reviewed by Dr. R. Lostritto
	III			3	Adequate	2/9/01	Reviewed by Dr. D. Klein
	III			3	Adequate	9/28/00	Reviewed by Dr. D. Klein
	III			3	Adequate	3/24/00	Reviewed by Dr. D. Klein
	III			3	Adequate	3/31/01	Reviewed by Dr. D. Lin
	III			3	Adequate	3/2/00	Reviewed by Dr. D. Christodoulou
	III			3	Adequate	12/4/00	Reviewed by Dr. M. Adams
	III			3	Adequate	8/11/00	Reviewed by Dr. R. Trimmer
	III			3	Adequate	4/20/00	Reviewed by Dr. S. Markosky

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Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Original NDA	NDA 4-782	Approved NDA for Premarin Tablets
Patent	5,210,081	Drug substance, drug product formulation, method of use. Expiration date: 2/26/2012. Patent owner: Wyeth-Ayerst Laboratories

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Withhold		M. Garcia
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Methods previously validated for approved strengths		
OPDRA	N/A		
EA	Categorical exclusion granted		David Lin, Ph.D.
Microbiology	N/A		

The Chemistry Review for NDA 21-417

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From chemistry, manufacturing, and controls point of view, this NDA is **Approvable.**

Before this application may be approved, it will be necessary to address the following:

- **The Wyeth Laboratories facility in Rouses Point, NY must have a satisfactory cGMP inspection. In addition, all facilities listed in this application must be in cGMP compliance.**

In addition, it is recommended that the storage statement in the Physician Insert and the container/carton labels be consistent and revised as follows: "Store at

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

Premarin® is a solid dosage form intended for oral administration. The currently approved dosage strength tablet for the treatment of osteoporosis is 0.625 mg conjugated estrogens, USP (CE). This NDA proposes to add two new strength tablets, 0.3 mg CE and 0.45 mg CE, for this indication. The 0.3 mg dosage strength is a green colored, oval, biconvex sugar coated tablet. The 0.45 mg dosage strength is a blue colored, oval, biconvex sugar coated tablet. The 0.3 mg dosage strength tablet is currently approved for the treatment of vulvar and vaginal atrophy.

The dosage form consists of a core tablet containing Conjugated Estrogens which is

The product is co-manufactured at the Ayerst Laboratories facility in Rouses Point, NY and the Wyeth Pharmaceuticals facility in Guayama, Puerto Rico.

The product quality is assured through the following release tests: 1) appearance, 2) potency of sodium estrone sulfate plus sodium equilin sulfate, 3) total conjugated estrogen content (sum of sodium estrone sulfate, sodium equilin sulfate, sodium 17α-dihydroequilin sulfate), 4) sodium equilin sulfate/sodium estrone sulfate ratio, 5) CE ID, 6) CE dissolution, and 7) content uniformity of CE. All the proposed specifications has been determined to be acceptable.

Executive Summary Section

The product will be packaged in [redacted] configurations: [redacted] (100 count) [redacted] bottles with a [redacted] The [redacted] packaging consists of [redacted]. The bottles are made from [redacted]. The [redacted] closures for the bottles consist of [redacted]. The market packaging configuration is the [redacted] bottle. [redacted] The relevant DMFs for the [redacted] have been reviewed and determined to be adequate for this product.

Based on the stability data provided for the 0.45 mg dosage strength tablet, a 24-month expiry date is granted, when stored at 25°C/60% RH (controlled room temperature). No additional data have been provided for the approved 0.3 mg dosage strength tablet, and therefore the expiry remains at 36 months when stored at controlled room temperature. Adequate chemistry information is presented in the physician and patient labeling, and labels of the primary as well as secondary packaging labels. However, the storage statement needs to be revised as recommended in this review.

Drug Substance:
Conjugated estrogens (CE) drug substance is a mixture of conjugated estrogens derived from the urine of pregnant mares. All the information relevant to the control of the manufacturing and quality of CE is referenced to NDA 4-782 (Premarin Tablets).

B. Description of How the Drug Product is Intended to be Used

A single tablet of Premarin® is to be orally administered daily for the prevention of bone loss in postmenopausal women with an intact uterus.

The drug product expiry for the 0.45 mg dosage strength is 24 months when stored at 20-25°C (controlled room temperature). The 0.3 mg dosage strength expiry is currently 36 months at the same storage condition.

C. Basis for Approvability or Not-Approval Recommendation

This NDA is Approvable from a CMC point of view, due to an unsatisfactory cGMP inspection at the Ayerst facility in Rouses Point, NY. A satisfactory inspection is required before this NDA may be approved. In addition, the other relevant manufacturing and testing sites need to remain in compliance with cGMP.

The only other minor CMC issue is the unacceptable storage statement in the Physician Insert and on the container/carton labels.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: YYang/DLin/
ChemistryTeamLeaderName: DLin
ProjectManagerName: SWu

C. CC Block

HFD-510/Division File/NDA 21-417
HFD-580/D.T. Lin, Ph.D.
HFD-510/S. Wu/YYang

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/s/

David T. Lin
10/7/02 04:43:24 PM
CHEMIST