CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-396

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-396
Review number: 1
Sequence number/date/type of submission: filed 11/24/01
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Wyeth-Ayerst; Philadelphia, PA
Manufacturer for drug substance : same

Reviewer name: Karen Davis-Bruno; Ph.D.
Division name: DMEDP
HFD #: 510
Review completion date: 6/7/02

Drug:

Trade name: Prempro/Premphase

Generic name (list alphabetically): conjugated estrogens[CE]/medroxyprogesterone acetate [MPA]

Relevant INDs/NDAs/DMFs: NDA 20-303

Drug class: conjugated estrogens and progesterone for hormone replacement therapy (HRT) in post menopausal women

Indication: prevention of osteoporosis

Clinical formulation: 0.45 mg CE/1.5 mg MPA; 0.3 mg CE/1.5 mg MPA

Route of administration: oral tablet

APPEARS THIS WAY
ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation on Approvability- Pharmacology/Toxicology recommends approval for the proposed doses and indication.

B. Recommendation for Nonclinical Studies- none

C. Recommendations on Labeling-none

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings The sponsor references approved NDA 20-303 for nonclinical studies. New information has not been submitted.

B. Pharmacologic Activity see approved NDA 20-303 for details.

C. Nonclinical Safety Issues Relevant to Clinical Use-There are no nonclinical safety issues with this proposed lower dose for prevention of osteoporosis. Higher doses have been approved for use in HRT and therefore the studies used to support safety of the higher doses adequately support these lower doses. See approved NDA 20-303 for details.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:

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III. PHARMACOKINETICS/TOXICOKINETICSERROR! BOOKMARK NOT DEFINED.

IV. GENERAL TOXICOLOGY: .....ERROR! BOOKMARK NOT DEFINED.

V. GENETIC TOXICOLOGY:.....ERROR! BOOKMARK NOT DEFINED.

VI. CARCINOGENICITY: .....ERROR! BOOKMARK NOT DEFINED.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY: .....N/A

VIII. SPECIAL TOXICOLOGY STUDIES: .....N/A

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:.....N/A

X. APPENDIX/ATTACHMENTS: .....ERROR! BOOKMARK NOT DEFINED.

Please refer to approved NDA 20-303 for nonclinical study details. Nonclinical information has not been submitted.

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/s/

Karen Davis-Bruno
6/7/02 01:27:22 PM
PHARMACOLOGIST

APPEARS THIS WAY
ON ORIGINAL

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-396
Review number: 1
Sequence number/date/type of submission:00
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Wyeth-Ayerst
Manufacturer for drug substance : same

Reviewer name: Karen Davis-Bruno; Ph.D.
Division name: DMEDP
HFD #: 510
Review completion date: 11/20/01

Drug:

Trade name: Premphase, Prempro
Generic name (list alphabetically): conjugated estrogens/medroxyprogesterone acetate
Code name: N/A
Chemical name: N/A
CAS registry number: not provided
Mole file number: not provided
Molecular formula/molecular weight: not provided
Structure: estrogen is not provided

Relevant INDs/NDAs/DMFs: NDA 20-303 is referenced

Drug class: oral contraceptives

Indication: osteoporosis

Clinical formulation:1) 0.45 mg CE/1.5 mg MPA
2) 0.3 mg CE/1.5 mg MPA
Route of administration: oral

Proposed use: in a continuous combined regimen for the prevention of osteoporosis

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Executive Summary

I. Recommendations

A. Recommendation on Approvability: Pharmacology recommends approval.

B. Recommendation for Nonclinical Studies: Prempro, Premphase (0.625 mg CE/2.5 or 5 mg MPA) was approved under NDA 20-303. The doses approved are higher than those suggested here. Additional nonclinical studies were not needed or provided. There is extensive nonclinical and clinical data available for this product.

C. Recommendations on Labeling: Labeling should be identical to the current label for Prempro, Premphase.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings: Prempro, Premphase (0.625 mg CE/2.5 or 5 mg MPA) was approved under NDA 20-303. The doses approved are higher than those suggested here. Additional nonclinical studies were not needed or provided. There is extensive nonclinical and clinical data available for this product.

B. Pharmacologic Activity not provided

C. Nonclinical Safety Issues Relevant to Clinical Use none

III. Administrative

A. Reviewer signature: _____
Supervisory Pharmacologist

B. Supervisor signature: Concurrence - NA

Non-Concurrence - _____
(see memo attached)

C. cc: list: HFD510/Davis-Bruno/Wu

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V. GENETIC TOXICOLOGY: 1

VI. CARCINOGENICITY: ..... ERROR! BOOKMARK NOT DEFINED.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY: 1

VIII. SPECIAL TOXICOLOGY STUDIES: 1

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS: 1

X. APPENDIX/ATTACHMENTS: 1

Reviewer: NDA No.

PHARMACOLOGY/TOXICOLOGY REVIEW

I. **PHARMACOLOGY:** Reference to approved NDA 21-396

II. **SAFETY PHARMACOLOGY:** Reference to approved NDA 21-396

III. **PHARMACOKINETICS/TOXICOKINETICS:** Reference to approved NDA 21-396

IV. **GENERAL TOXICOLOGY:** Reference to approved NDA 21-396

IV. **GENETIC TOXICOLOGY:** Reference to approved NDA 21-396

V. **CARCINOGENICITY:** Reference to approved NDA 21-396

VII. **REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:** Reference to approved NDA 21-396

VIII. **SPECIAL TOXICOLOGY STUDIES:** Reference to approved NDA 21-396

IX. **DETAILED CONCLUSIONS AND RECOMMENDATIONS**

Conclusions: Prempro, Premphase (0.625 mg CE/2.5 or 5 mg MPA) was approved under NDA 20-303. The doses approved are higher than those suggested here. Additional nonclinical studies were not needed or provided. There is extensive nonclinical and clinical data available for this product.

General Toxicology Issues: none

Recommendations: approval

Labeling with basis for findings: current Prempro, Premphase label is adequate

X. **APPENDIX/ATTACHMENTS: NOT APPLICABLE**

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/s/

Karen Davis-Bruno
11/20/01 04:36:07 PM
PHARMACOLOGIST
P/T NDA review

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-396
Submission Dates	September 24, 2001
Brand Name	PREMPRO™
Generic Name	conjugated estrogens and medroxyprogesterone acetate
Reviewer	S.W. Johnny Lau
Team Leader	Hae-Young Ahn
OCPB Division	DPE II (HFD-870)
ORM division	Metabolic and Endocrine Drug Products (HFD-510)
Sponsor	Wyeth-Averst Research.
Relevant IND(s)	21,696
Submission Type: Code	Efficacy: SE2
Formulation: Strength(s)	Film-coated tablets 0.45 mg/1.5 mg and 0.3 mg/1.5 mg
Indication	To prevent postmenopausal osteoporosis

Executive Summary

In NDA 21-396 SE2, sponsor proposed 2 oral tablets, 0.45 mg conjugated estrogens (CE) with 1.5 mg medroxyprogesterone acetate (MPA) or 0.3 mg CE with 1.5 mg MPA, in a continuous combined regimen for the prevention of osteoporosis and submitted the NDA on September 24, 2001 to the Division of Metabolic and Endocrine Drug Products (HFD-510). Sponsor also proposed the same 2 oral tablets in a continuous combined regimen to the Division of Reproductive and Urologic Drug Products (HFD-580) for the treatment of moderate to severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy on June 15, 2000 via NDA 20-527 SLR-017, which is approvable pending manufacturing issues.

PREMPRO™/PREMPHASE® is approved for the treatment of vasomotor symptoms, and vulvar and vaginal atrophy associated with menopause and for the prevention of osteoporosis with doses of 0.625 mg CE/2.5 mg MPA and 0.625 mg CE/5.0 mg MPA. PREMPRO™ is the trade name of the continuous combined regimen whereas PREMPHASE® is a cyclic regimen.

The Human Pharmacokinetics and Bioavailability section for NDA 21-396 SE2 is identical to that for NDA 20-527 SLR-017. Therefore, the review for the Human Pharmacokinetics and Bioavailability section of NDA 21-396 SE2 will be referred to that for NDA 20-527 SLR-017.

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) reviewed NDA 21-396 SE2. OCPB finds that the submitted information supports the Human Pharmacokinetics and Bioavailability section and the Clinical Pharmacology section of labeling for NDA 21-396 SE2. Please convey the recommendation and comments as appropriate.

Comments

- Sponsor's proposed conjugated estrogens in vitro dissolution method (USP XXIV apparatus 2, 900 mL water, 37°C, and 50 rpm) is acceptable. However, the recommended conjugated estrogens in vitro dissolution specifications for the 0.45 mg conjugated estrogens/1.5 mg

medroxyprogesterone acetate and 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate oral tablets are:

Time	% estrone sulfate released
[redacted]	

Sponsor accepted the recommended conjugated estrogens in vitro dissolution specifications per sponsor's April 12, 2001 letter for NDA 20-527 SLR-017.

- Sponsor's proposed medroxyprogesterone acetate in vitro dissolution method via USP disintegration apparatus (0.54% sodium lauryl sulfate, 900 mL, 37°C, and 30 dips/min) is acceptable on an interim basis. The recommended medroxyprogesterone acetate specification for the 0.45 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate and 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate oral tablets are:

Time	% medroxyprogesterone acetate released
30 minutes	Not less than [redacted] Q = [redacted])

[redacted]

- Sponsor's Clinical Pharmacology labeling changes per teleconference on April 12, 2001 for NDA 20-527 SLR-017 are acceptable.

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

FT signed by Hae-Young Ahn, Ph.D., Team Leader 7/ /02

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/s/

S.W. Johnny Lau
7/17/02 05:03:30 PM
BIOPHARMACEUTICS

Hae-Young Ahn
7/17/02 05:33:09 PM
BIOPHARMACEUTICS