CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 21-396

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Filing Memo

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS	
NDA:	**21-396**
Compound:	0.45 or 0.3 mg conjugated estrogens and 1.5 mg medroxyprogesterone acetate
Sponsor:	Wyeth-Ayerst Research
Submission Date:	September 24, 2001
From:	S.W. Johnny Lau, R.Ph., Ph.D.

Background:

Sponsor submitted NDA 21-396 to seek approval for the 0.45 mg conjugated estrogens (CE)/1.5 mg medroxyprogesterone acetate (MPA) or 0.3 mg CE/1.5 mg MPA oral tablets to be administered in a continuous combined regimen for the prevention of osteoporosis. The 0.45 mg CE/1.5 mg MPA is deemed approvable to treat moderate to severe vasomotor symptoms associated with menopause, and [redacted] vulvar and vaginal atrophy under NDA 20-527 SLR-017 by the Division of Reproductive and Urologic Drug Products on April 13, 2001. Sponsor [redacted] oral tablet under NDA 20-527 SLR-017. Per chemistry team leader, Dr. David Lin (HFD-580), the formulations (0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA oral tablets) submitted for NDA 21-396 and NDA 20-527 SLR-017 are identical. Similar clinical pharmacology information was presented in NDA 21-396. See the clinical pharmacology and biopharmaceutics review for both 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA oral tablets under NDA 20-527 SLR-017 for details.

Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) found that the Human Pharmacokinetics and Bioavailability section of NDA 21-396 is fileable.

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

FT signed by Hae-Young Ahn, Ph.D., Team Leader _____ 11/ /01

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/s/

S.W. Johnny Lau
11/30/01 09:41:59 AM
BIOPHARMACEUTICS

Hae-Young Ahn
11/30/01 01:06:36 PM
BIOPHARMACEUTICS

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)	—
Submission Type: Code	Efficacy: —
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 — 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 — 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 tr — vasomotor symptoms. — 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 — is identical to that for NDA 20-527 SLR-017. Therefore, the review for the Human Pharmacokinetics and Bioavailability section of NDA 21-396 — 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 — OCPB finds that the submitted information supports the Human Pharmacokinetics and Bioavailability section and the Clinical Pharmacology section of labeling for NDA 21-396 — 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
2 hours	[redacted]
5 hours	[redacted]
8 hours	[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	[redacted]

Sponsor accepted the recommended medroxyprogesterone acetate in vitro disintegration specifications per sponsor's April 11, 2001 letter for NDA 20-527 SLR-017.

- [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

APPEARS THIS WAY
ON ORIGINAL