

021396 - Original - Approval - Pkg

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 21-396

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Final Printed Labeling	✓
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Pharmacology Review(s)	✓
Statistical Review(s)	✓
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Approval Package for:

Application Number 21-396

Trade Name Prempro / Premphase .45mg/1.5mg + .3mg/1.5mg

Generic Name Conjugated estrogens / medroxyprogesterone acetate

Sponsor Wyeth

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-396

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-396

Wyeth Pharmaceuticals
Attention: Jennifer D. Norman, RPh
Associate Director, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Norman:

Please refer to your new drug application (NDA) dated September 24, 2001, received September 25, 2001, submitted under Section 505b(1) of the Federal Food, Drug, and Cosmetic Act for Prempro™/Premphase® (conjugated estrogens/medroxyprogesterone acetate tablets) 0.45mg/1.5mg and 0.3mg/1.5mg.

We acknowledge receipt of your submissions dated November 18, December 3, 2002, April 2, and May 30, 2003.

The December 3, 2002 submission constituted a complete response to our July 25, 2002 action letter.

This new drug application provides for the use of Prempro™/Premphase® (conjugated estrogens/medroxyprogesterone acetate tablets) 0.45mg/1.5mg and 0.3mg/1.5mg for the prevention of postmenopausal osteoporosis.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert and patient package insert) and submitted labeling, (immediate container and carton labels submitted September 24, 2001). Marketing the products with FPL that is not identical to the approved labeling text may render the products misbranded and unapproved new drugs.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved NDA 21-396." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA (NDA 20-527). In the future, do not make submissions to this NDA except for the final printed labeling requested above.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 827-6416.

Sincerely,

{See appended electronic signature page}

David G.Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures: package insert
patient package insert

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/s/

David Orloff
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-396

APPROVABLE LETTER



NDA 21-396

Wyeth-Ayerst Laboratories
Attention: Jennifer D. Norman, R.Ph.
Associate Director, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

JUL 25 2002

Dear Ms. Norman:

Please refer to your new drug application (NDA) dated September 24, 2001, received September 25, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prempro™/Premphase® (conjugated estrogens/medroxyprogesterone acetate tablets) 0.45mg/1.5mg and 0.3mg/1.5mg.

We acknowledge receipt of your submissions dated November 13, 2001, January 24 and 25, February 1, April 23, May 29, and June 17, 18, and 26, 2002.

We have completed the review of this application, as amended, and it is approvable.

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

1. Taking into account the results of the Women's Health Initiative (WHI) study that were reported in the July 17, 2002, issue of JAMA, please provide an updated risk/benefit analysis of the 0.45mg/1.5mg and 0.3mg/1.5mg doses of Prempro™/Premphase® when used in the prevention of postmenopausal osteoporosis.
2. Provide detailed analyses of the cardiovascular adverse event data from the HOPE trial. To the extent possible, the analyses should parallel those from the WHI study that were reported in the July 17, 2002, issue of JAMA. Consultation with DMEDP is strongly encouraged as you undertake the analyses.

In addition, during recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted. Before this application may be approved, all manufacturing facilities must obtain a satisfactory cGMP inspection.

The labeling for this product will be discussed at a later date.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required. Specifically, we anticipate changes relating to the recently published WHI study.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

NDA 21-396
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If you have any questions, call Samuel Y. Wu, Pharm.D., Regulatory Project Manager,
at 301-827-6416.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

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this page is the manifestation of the electronic signature.**

/s/

David Orloff
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