DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020472/S-011

SUPPLEMENT APPROVAL

Pharmacia & Upjohn Company
c/o Pfizer Inc.
Attention: Michele Burtness
Worldwide Safety and Regulatory
235 East 42nd Street
New York, NY 10017

Dear Ms. Burtness:

Please refer to your Supplemental New Drug Application (sNDA) dated June 20, 2013, received June 21, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Estring® (estradiol vaginal ring).

We acknowledge receipt of your amendments dated September 24, November 15, 2013, and February 14, and April 30, 2014.

This supplemental new drug application provides for the addition of Cases of Hypersensitivity to the Post-marketing Experience section of the Physician Information and the related update to the Patient Information.

This non-PLR format labeling was revised to update the following sections:

FULL PRESCRIBING INFORMATION

- Updated the Boxed Warning to include a revised general heading and two specific subheadings: Estrogen-Alone Therapy and Estrogen Plus Progestin Therapy; updated the text in the Boxed Warning to reflect the current recommended estrogen-class labeling.
- Updated the text in the CLINICAL PHARMACOLOGY Section to reflect the current recommended estrogen-class labeling under Specific Populations: “No pharmacokinetic studies were conducted with ESTRING in specific populations, including women with renal or hepatic impairment.”
- Added under the CLINICAL STUDIES Section, Women’s Health Initiative Studies Subsection, the Subheading *WHI Estrogen-Alone Substudy*; revised and updated Table 2; added the following recommended estrogen-class labeling:
  - “No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE alone compared with

placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow-up of 7.1 years."
- "Timing of initiation of estrogen-alone therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen-alone substudy stratified by age showed in women 50 to 59 years of age a non-significant trend toward reduced risk for CHD *[hazard ratio (HR) 0.63 (95 percent CI, 0.36-1.09)]* and overall mortality *[HR 0.71 (95 percent CI, 0.46–1.11)]."*

- Added under the CLINICAL STUDIES Section, Women's Health Initiative Studies Subsection, the Subheading *WHI Estrogen Plus Progestin Substudy*; revised and updated Table 3; added the following recommended estrogen-class labeling:
  - Timing of initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified by age showed in women 50 to 59 years of age a non-significant trend toward reduced risk for overall mortality [HR 0.69 (95 percent CI, 0.44-1.07)]."
- Updated the text under the CLINICAL STUDIES Section, Women's Health Initiative Memory Study Subsection to reflect the current recommended estrogen class labeling.
- Modified the text under the INDICATIONS AND USAGE Section to reflect the current recommended estrogen class labeling.
  From:
  "ESTRING (estradiol vaginal ring) is an estrogen indicated for the treatment of moderate to severe urogenital symptoms due to postmenopausal atrophy of the vagina (such as dryness, burning, pruritus and dyspareunia) and/or the lower urinary tract (urinary urgency and dysuria)."
  To:
  - ESTRING is indicated for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause."
- Modified the CONTRAINDICATIONS Section by adding as bullet number 6:
  - "Known anaphylactic reaction or angioedema or hypersensitivity to ESTRING."
- Modified the CONTRAINDICATIONS Section by adding as bullet number 8:
  - "Known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders."
- Updated the WARNINGS Section, Subsection 1. Cardiovascular Disorders by including the following information under a. Stroke:
  - "Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years)."
- Updated the WARNINGS Section, Subsection 1. Cardiovascular Disorders by including the following information under b. Coronary Heart Disease:
  - "Subgroup analyses of women 50 to 59 years of age suggest a statistically nonsignificant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years)."
- Updated the WARNINGS Section, Subsection 2. Malignant Neoplasms under b. Breast Cancer to reflect the current recommended estrogen-class labeling.
- Updated the WARNINGS Section, Subsection 3. Probable Dementia to reflect current recommended estrogen-class labeling.

- Added to the WARNINGS Section:
  - 7. Hereditary Angioedema
  "Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema."
- Updated the PRECAUTIONS Section, Subsection I. Geriatric Use, to reflect the findings in *The Women's Health Initiative Studies* and *The Women's Health Initiative Memory Study*; accompanying text was modified to reflect current recommended estrogen-class labeling.
- Updated the PRECAUTIONS Section, as appropriate, to reflect current recommended estrogen-class labeling.
- Accepted your proposed revisions to the ADVERSE REACTIONS Section under Post-Marketing Experience.

PATIENT INFORMATION LEAFLET

- Updated the Boxed Warning to match the Boxed Warning text in the Full Prescribing Information labeling; modified the accompanying text to include current recommended estrogen-class labeling
- Modified the text under "What is ESTRING used for?" to read: "ESTRING is used after menopause to treat moderate to severe menopausal changes in and around the vagina."
- Under "Who should not use ESTRING?" added the following text under bullet 1: "Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause."
- Added as bullet 6 "Have been diagnosed with a bleeding disorder" under "Who should not use ESTRING?"
- Under "Who should not use ESTRING?" added the following text under bullet 8: "ESTRING is not for pregnant women. If you think you may be pregnant, you should have a pregnancy test and know the results. Do not use ESTRING if the test is positive and talk to your healthcare provider.
- Modified "What should I tell my healthcare provider before I use ESTRING?" to reflect current recommended estrogen class labeling.
- Relocated "How should I use ESTRING" to follow "What are the Ingredients in ESTRING" under Instruction for Use at the end of the Patient Information Insert.
- Reorder the listings under "What are the possible side effects of ESTRING?" to reflect current recommended estrogen-class labeling.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text which also includes the minor editorial revision listed below.

- Revision date of August 2014, not May 2014

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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

If you have any questions, call Kim Shiley, R.N., B.S.N., Regulatory Project Manager, at (301) 796-2117.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Deputy Director
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AUDREY L GASSMAN
08/12/2014