CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20216Orig1s060

Trade Name: **PREMARIN**

Generic Name: conjugated estrogens

Sponsor: Wyeth Pharmaceuticals Inc.

Approval Date: 11/07/2008

Indications: PREMARIN (conjugated estrogens) Vaginal Cream is a mixture of estrogens indicated for:

- Treatment of Atrophic Vaginitis and Kraurosis Vulvae
- Treatment of Moderate to Severe Dyspareunia, a Symptom of a Vulvar and Vaginal Atrophy, due to Menopause

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20216Orig1s060

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-216/S-060

Wyeth Pharmaceuticals Inc.
Attention: Donald Lewis, Manager
Global Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19102-8299

Dear Mr. Lewis:

Please refer to your supplemental new drug application dated September 25, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Premarin® (conjugated estrogens) Vaginal Cream.

We acknowledge receipt of your submissions dated September 4, November 4, 5, and 6, 2008.

Your submission of September 4, 2008, received on September 5, 2008, constituted a complete response to our July 25, 2008 action letter.

This supplemental new drug application provides for the use of Premarin® (conjugated estrogens) Vaginal Cream for (1) a new indication, the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause and (2) a new dosing regimen for this indication, 0.5 g Premarin® (conjugated estrogens) Vaginal Cream intravaginally twice weekly.

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

The final printed labeling (FPL) must be identical to the enclosed labeling and to the immediate container and carton labels submitted on November 4 and 5, 2008.

We are waiving the requirement of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed, agreed-upon labeling. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 20-216/S-060**."

PEDIATRIC RESEARCH EQUITY ACT (PREA)

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.

We are waiving the pediatric study requirement for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause because studies are impossible given the lack of pediatric patients with this condition.

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 George Lyght, R.Ph., Sr. Regulatory Project Manager, at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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

/s/

Scott Monroe

11/7/2008 03:46:14 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20216Orig1s060

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-216/S-060

Wyeth Pharmaceuticals Inc.
Attention: Donald Lewis, Manager
Global Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19102-8299

Dear Mr. Lewis:

Please refer to your supplemental new drug application dated September 25, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Premarin® (conjugated estrogens) Vaginal Cream.

We acknowledge receipt of your submissions dated November 9 and 21, December 13, 2007, January 25, February 11, March 4 and 25, April 1, 4, 11, 16 and 30, May 23 and July 14, 2008.

This supplemental new drug application provides for the use of Premarin® (conjugated estrogens) Vaginal Cream for (1) a new indication, the treatment of dyspareunia associated with vulvar vaginal atrophy (VVA) and (2) a new dosing regimen option, 0.5 g twice weekly.

We have completed our review of this application, as amended, and it is approvable because labeling remains unresolved. Because we have failed to come to agreement on the labeling, including the indication section, we will continue discussions based on the version we sent to you on July 2, 2008.

If additional information relating to the safety or effectiveness of this drug becomes available, additional revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. 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.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with the Division of Reproductive and Urologic Products to discuss what further steps need to be taken before the application may be approved.

This product may be considered misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes before approval of this supplemental application.

If you have any questions, call George Lyght, R.Ph., Sr. Regulatory Health Project Manager, at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Scott Monroe

7/25/2008 04:35:25 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20216Orig1s060

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PREMARIN Vaginal Cream safely and effectively. See full prescribing information for PREMARIN Vaginal Cream.

PREMARIN (conjugated estrogens) Vaginal Cream
Initial U.S. approval: 1946

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS AND PROBABLE DEMENTIA FOR ESTROGEN-ALONE THERAPY

See full prescribing information for complete boxed warning.

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. (5.3)**
- **Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia. (5.2, 5.4)**
- **The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis. (5.2)**
- **The Women's Health Initiative Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older. (5.4)**

WARNING: CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA FOR ESTROGEN PLUS PROGESTIN THERAPY

See full prescribing information for complete boxed warning.

- **Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia. (5.2, 5.4)**
- **The WHI estrogen plus progestin substudy reported increased risks of stroke, deep vein thrombosis, pulmonary embolism, and myocardial infarction. (5.2)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer. (5.3)**
- **The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older. (5.4)**

---------- RECENT MAJOR CHANGES ----------

Indications and Usage (1)	11/2008
Dosage and Administration (2.3)	11/2008
Warnings and Precautions:	
- Malignant Neoplasms, Ovarian Cancer (5.3)	3/2008

---------- INDICATIONS AND USAGE ----------

PREMARIN (conjugated estrogens) Vaginal Cream is a mixture of estrogens indicated for:

- Treatment of Atrophic Vaginitis and Kraurosis Vulvae (1.1)
- Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause (1.2)

----------DOSAGE AND ADMINISTRATION ----------

- Cyclic administration of 0.5 to 2 g intravaginally [daily for 21 days then off for 7 days] for Treatment of Atrophic Vaginitis and Kraurosis Vulvae (2.2)
- Cyclic administration of 0.5 g intravaginally [daily for 21 days then off for 7 days] for Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause (2.3)
- Twice-weekly administration of 0.5 g intravaginally [for example, Monday and Thursday] for Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Each gram contains 0.625 mg conjugated estrogens, USP (3)
- *Combination package* Each contains a net wt. 1.5 oz (42.5 g) tube with one plastic applicator calibrated in 0.5 g increments to a maximum of 2 g (3)

---------- CONTRAINDICATIONS ----------

- Undiagnosed abnormal genital bleeding (4)
- Known, suspected, or history of breast cancer (4, 5.3)
- Known or suspected estrogen-dependent neoplasia (4, 5.3)
- Active deep vein thrombosis, pulmonary embolism or a history of these conditions (4, 5.2)
- Active arterial thromboembolic disease (for example, stroke, myocardial infarction) or a history of these conditions (4, 5.2)
- Known liver dysfunction or disease (4, 5.10)
- Known or suspected pregnancy (4, 8.1)

---------- WARNINGS AND PRECAUTIONS ----------

- Estrogens increase the risk of gallbladder disease (5.5)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.6, 5.7, 5.10, 5.11)
- Monitor thyroid function in women on thyroid replacement therapy (5.12, 5.19)

---------- ADVERSE REACTIONS ----------

In a prospective, randomized, placebo-controlled, double-blind study, the most common adverse reactions ≥ 5 percent are headache, infection, abdominal pain, back pain, accidental injury, and vaginitis. (6.1, 14.1)

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-934-5556 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- DRUG INTERACTIONS ----------

Inducers and/or inhibitors of CYP3A4 may affect estrogen drug metabolism (7)

---------- USE IN SPECIFIC POPULATIONS ----------

- Nursing Women: Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk. (8.3)
- Geriatric Use: An increased risk of probable dementia in women over 65 years of age was reported in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative. (5.4, 8.5)

See 17 for Patient Counseling Information and FDA-approved patient labeling

Revised: 11/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS AND PROBABLE DEMENTIA FOR ESTROGEN-ALONE THERAPY

ENDOMETRIAL CANCER

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding *[see Warnings and Precautions (5.3)]*.

CARDIOVASCULAR DISORDERS AND PROBABLE DEMENTIA

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3)]*.

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg], relative to placebo *[see Warnings and Precautions (5.2), and Clinical Studies (14.2)]*.

The Women's Health Initiative Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg) alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

WARNING: CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA FOR ESTROGEN PLUS PROGESTIN THERAPY

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3)]*.

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism, stroke and myocardial infarction in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo *[see Warnings and Precautions (5.2), and Clinical Studies (14.2)]*.

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions (5.3), and Clinical Studies (14.2)]*.

The WHIMS estrogen plus progestin ancillary study of the WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

1 INDICATIONS AND USAGE

1.1 Treatment of Atrophic Vaginitis and Kraurosis Vulvae

1.2 Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be considered to reduce the risk of endometrial cancer.

A woman without a uterus does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin *[see Warnings and Precautions (5.3, 5.15)]*.

Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

2.2 Treatment of Atrophic Vaginitis and Kraurosis Vulvae

PREMARIN Vaginal Cream is administered intravaginally in a cyclic regimen (daily for 21 days and then off for 7 days). Generally, women should be started at the 0.5 g dosage strength. Dosage adjustments (0.5 to 2 g) may be made based on individual response *[see Dosage Forms and Strengths (3)]*.

2.3 Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause

PREMARIN Vaginal Cream (0.5 g) is administered intravaginally in a twice-weekly (for example, Monday and Thursday) continuous regimen or in a cyclic regimen of 21 days of therapy followed by 7 days off of therapy *[see Dosage Forms and Strengths (3)]*.

3 DOSAGE FORMS AND STRENGTHS

Each gram contains 0.625 mg conjugated estrogens, USP.

Combination package Each contains a net wt. 1.5 oz (42.5 g) tube with one plastic applicator calibrated in 0.5 g increments to a maximum of 2 g.

4 CONTRAINDICATIONS

PREMARIN Vaginal Cream therapy should not be used in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active deep vein thrombosis, pulmonary embolism or a history of these conditions
- Active arterial thromboembolic disease (for example, stroke, and myocardial infarction), or a history of these conditions
- Known liver dysfunction or disease
- Known or suspected pregnancy

5 WARNINGS AND PRECAUTIONS

5.1 Risks From Systemic Absorption

Systemic absorption occurs with the use of PREMARIN Vaginal Cream. The warnings, precautions, and adverse reactions associated with oral PREMARIN treatment should be taken into account.

5.2 Cardiovascular Disorders

An increased risk of stroke and deep vein thrombosis (DVT) has been reported with estrogen-alone therapy. An increased risk of pulmonary embolism, DVT, stroke and myocardial infarction has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogens with or without progestins should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (for example, personal history of venous thromboembolism [VTE], obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke

In the Women's Health Initiative (WHI) estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year one and persisted *[see Clinical Studies (14.2)]*. Should a stroke occur or be suspected, estrogens should be discontinued immediately.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg) versus those receiving placebo (18 versus 21 per 10,000 women-years).[1]

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in all women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to placebo (33 versus 25 per 10,000 women-years) *[see Clinical Studies (14.2)]*. The increase in risk was demonstrated after the first year and persisted.[1]

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal myocardial infarction [MI], silent MI, or CHD death) was reported in women receiving estrogen alone compared to placebo[2] *[see Clinical Studies (14.2)]*.

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE 0.625 mg compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).[1]

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years).[1] An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 *[see Clinical Studies (14.2)]*.

In postmenopausal women with documented heart disease (n = 2,763), average age 66.7 years, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during subsequent users. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE (0.625 mg) plus MPA (2.5 mg) group and the placebo group in HERS, HERS II, and overall.

Venous Thromboembolism (VTE)

In the WHI estrogen-alone substudy, the risk of VTE (DVT and pulmonary embolism [PE]) was increased for women receiving daily CE (0.625 mg) compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years[3] *[see Clinical Studies (14.2)]*. Should a VTE occur or be suspected, estrogens should be discontinued immediately.

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was observed during the first year and persisted[4] *[see Clinical Studies (14.2)]*. Should a VTE occur or be suspected, estrogens should be discontinued immediately.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

5.3 Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

In a 52-week clinical trial using PREMARIN Vaginal Cream alone (0.5 g inserted twice weekly or daily for 21 days, then off for 7 days), there was no evidence of endometrial hyperplasia or endometrial carcinoma.

Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the Women's Health Initiative (WHI) substudy of daily CE (0.625 mg). In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE (0.625 mg) was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80)[5] *[see Clinical Studies (14.2)]*.

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for estrogen plus progestin compared with placebo.[6] Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years for estrogen plus progestin compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for estrogen plus progestin compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups *[see Clinical Studies (14.2)]*.

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms, requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo, was 1.58 (95 percent nCI 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.[7] In some epidemiologic studies, the use of estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association.

5.4 Probable Dementia

In the estrogen-alone Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg) or placebo. In the WHIMS estrogen plus progestin ancillary study, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo.

In the WHIMS estrogen-alone ancillary study, after an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent nCI 0.83-2.66). The absolute risk of probable dementia for CE alone versus placebo was 37 versus 25 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.3), and Clinical Studies (14.3)]*.

In the WHIMS estrogen plus progestin ancillary study, after an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent nCI 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.3), and Clinical Studies (14.3)]*.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent nCI 1.19-2.60). Since both substudies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

5.5 Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

5.6 Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

5.7 Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

5.8 Addition of a Progestin When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration or daily with estrogen in a continuous regimen have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

5.9 Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen.

5.10 Hypertriglyceridemia

In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

5.11 Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

5.12 Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

5.13 Fluid Retention

Estrogens may cause some degree of fluid retention. Patients with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

5.14 Hypocalcemia

Estrogens should be used with caution in individuals with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

5.15 Exacerbation of Endometriosis

A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

5.16 Exacerbation of Other Conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

5.17 Effects on Barrier Contraception

PREMARIN Vaginal Cream exposure has been reported to weaken latex condoms. The potential for PREMARIN Vaginal Cream to weaken and contribute to the failure of condoms, diaphragms, or cervical caps made of latex or rubber should be considered.

5.18 Laboratory Tests

Serum follicle stimulating hormone and estradiol levels have not been shown to be useful in the management of moderate to severe symptoms of vulvar and vaginal atrophy.

5.19 Drug/Laboratory Test Interactions

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentrations, increased triglyceride levels.

Impaired glucose tolerance.

6 ADVERSE REACTIONS

6.1 Clinical Study Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a 12-week, randomized, double-blind, placebo-controlled trial of PREMARIN Vaginal Cream (PVC), a total of 423 postmenopausal women received at least 1 dose of study medication and were included in all safety analyses: 143 women in the PVC-21/7 treatment group (0.5 g PVC daily for 21 days, then 7 days off), 72 women in the matching placebo treatment group; 140 women in the PVC-2x/wk treatment group (0.5 g PVC twice weekly), 68 women in the matching placebo treatment group. A 40-week, open-label extension followed, in which a total of 394 women received treatment with PVC, including those subjects randomized at baseline to placebo. In this study, the most common adverse reactions ≥ 5 percent are shown below (Table 1) *[see Clinical Studies (14.1)]*.

Table 1: Number (%) of Patients Reporting Treatment Emergent Adverse Events ≥ 5 Percent Only

	Treatment			
Body System[a] Adverse Event	PVC 21/7 (n=143)	Placebo 21/7 (n=72)	PVC 2x/wk (n=140)	Placebo 2x/wk (n=68)
	Number (%) of Patients with Adverse Event			
Any Adverse Event	95 (66 4)	45 (62 5)	97 (69 3)	46 (67 6)
Body As A Whole				
Abdominal Pain	11 (7 7)	2 (2 8)	9 (6 4)	6 (8 8)
Accidental Injury	4 (2 8)	5 (6 9)	9 (6 4)	3 (4 4)
Asthenia	8 (5 6)	0	2 (1 4)	1 (1 5)
Back Pain	7 (4 9)	3 (4 2)	13 (9 3)	5 (7 4)
Headache	16 (11 2)	9 (12 5)	25 (17 9)	12 (17 6)
Infection	7 (4 9)	5 (6 9)	16 (11 4)	5 (7 4)
Pain	10 (7 0)	3 (4 2)	4 (2 9)	4 (5 9)
Cardiovascular System				
Vasodilatation	5 (3 5)	4 (5 6)	7 (5 0)	1 (1 5)
Digestive System				
Diarrhea	4 (2 8)	2 (2 8)	10 (7 1)	1 (1 5)
Nausea	5 (3 5)	4 (5 6)	3 (2 1)	3 (4 4)
Musculoskeletal System				
Arthralgia	5 (3 5)	5 (6 9)	6 (4 3)	4 (5 9)
Nervous System				
Insomnia	6 (4 2)	3 (4 2)	4 (2 9)	4 (5 9)
Respiratory System				
Cough Increased	0	1 (1 4)	7 (5 0)	3 (4 4)
Pharyngitis	3 (2 1)	2 (2 8)	7 (5 0)	3 (4 4)
Sinusitis	1 (0 7)	3 (4 2)	2 (1 4)	4 (5 9)
Skin And Appendages	12 (8 4)	7 (9 7)	16 (11 4)	3 (4 4)
Urogenital System				
Breast Pain	8 (5 6)	1 (1 4)	4 (2 9)	0
Leukorrhea	3 (2 1)	2 (2 8)	4 (2 9)	6 (8 8)
Vaginitis	8 (5 6)	3 (4 2)	7 (5 0)	3 (4 4)

[a] Body system totals are not necessarily the sum of the individual adverse events, since a patient may report two or more different adverse events in the same body system

6.2 Postmarketing Experience

The following adverse reactions have been reported with PREMARIN Vaginal Cream. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Genitourinary System

Abnormal uterine bleeding/spotting, dysmenorrhea/pelvic pain, increase in size of uterine leiomyomata, vaginitis (including vaginal candidiasis), change in cervical secretion, cystitis-like syndrome, application site reactions of vulvovaginal discomfort, (including burning, irritation, and genital pruritus), endometrial hyperplasia, endometrial cancer, precocious puberty, leukorrhea.

Breasts

Tenderness, enlargement, pain, discharge, fibrocystic breast changes, breast cancer, gynecomastia in males.

Cardiovascular

Deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, increase in blood pressure.

Gastrointestinal

Nausea, vomiting, abdominal cramps, bloating, increased incidence of gallbladder disease.

Skin

Chloasma that may persist when drug is discontinued, loss of scalp hair, hirsutism, rash.

Eyes

Retinal vascular thrombosis, intolerance to contact lenses.

Central Nervous System

Headache, migraine, dizziness, mental depression, nervousness, mood disturbances, irritability, dementia.

Miscellaneous

Increase or decrease in weight, glucose intolerance, edema, arthralgias, leg cramps, changes in libido, urticaria, anaphylactic reactions, exacerbation of asthma, increased triglycerides, hypersensitivity.

Additional postmarketing adverse reactions have been reported in patients receiving other forms of hormone therapy.

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted for PREMARIN Vaginal Cream.

7.1 Metabolic Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's Wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice, may increase plasma concentrations of estrogens and may result in side effects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

PREMARIN Vaginal Cream should not be used during pregnancy *[see Contraindications (4)]*. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

8.3 Nursing Mothers

PREMARIN Vaginal Cream should not be used during lactation. Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogens have been identified in the breast milk of mothers receiving estrogens. Caution should be exercised when PREMARIN Vaginal Cream is administered to a nursing woman.

8.4 Pediatric Use

PREMARIN Vaginal Cream is not indicated in children. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing PREMARIN Vaginal Cream to determine whether those over 65 years of age differ from younger subjects in their response to PREMARIN Vaginal Cream.

The Women's Health Initiative Study

In the Women's Health Initiative (WHI) estrogen-alone substudy (daily conjugated estrogens 0.625 mg versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age *[see Clinical Studies (14.2)]*.

In the WHI estrogen plus progestin substudy, there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65years of age *[see Clinical Studies (14.2)]*.

The Women's Health Initiative Memory Study

In the Women's Health Initiative Memory Study (WHIMS) of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in the estrogen-alone and the estrogen plus progestin substudies when compared to placebo *[see Clinical Studies (14.3)]*.

Since both substudies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Clinical Studies (14.3)]*.

8.6 Renal Impairment

The effect of renal impairment on PREMARIN Vaginal Cream pharmacokinetics has not been studied.

8.7 Hepatic Impairment

The effect of hepatic impairment on PREMARIN Vaginal Cream pharmacokinetics has not been studied.

10 OVERDOSAGE

Overdosage of estrogen may cause nausea and vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue, and withdrawal bleeding in females. Treatment of overdose consists of discontinuation of PREMARIN therapy with institution of appropriate symptomatic care.

11 DESCRIPTION

Each gram of PREMARIN (conjugated estrogens) Vaginal Cream contains 0.625 mg conjugated estrogens, USP in a nonliquefying base containing cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, benzyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil. PREMARIN Vaginal Cream is applied intravaginally.

PREMARIN Vaginal Cream contains a mixture of conjugated estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, sodium sulfate conjugates, 17 α-dihydroequilin, 17 α-estradiol, and 17 β-dihydroequilin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, which is secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

12.2 Pharmacodynamics

Currently, there are no pharmacodynamic data known for PREMARIN Vaginal Cream.

12.3 Pharmacokinetics

Absorption

Conjugated estrogens are water soluble and are well-absorbed through the skin, mucous membranes, and the gastrointestinal (GI) tract. The vaginal delivery of estrogens circumvents first-pass metabolism.

A bioavailability study was conducted in 24 postmenopausal women with atrophic vaginitis. The mean (SD) pharmacokinetic parameters for unconjugated estrone, unconjugated estradiol, total estrone, total estradiol and total equilin following 7 once-daily doses of PREMARIN Vaginal Cream 0.5 g is shown in Table 2.

Table 2: Mean ± SD Pharmacokinetic Parameters of PREMARIN Following Daily Administration (7 Days) of PREMARIN Vaginal Cream 0.5 g in 24 Postmenopausal Women			
Pharmacokinetic Profiles of Unconjugated Estrogens PREMARIN Vaginal Cream 0.5 g			
PK Parameters Arithmetic Mean ± SD	**C_{max} (pg/mL)**	**T_{max} (hr)**	**AUC_{ss} (pg•hr/mL)**
Estrone	42 0 ± 13 9	7 4 ± 6 2	826 ± 295
Baseline-adjusted estrone	21 9 ± 13 1	7 4 ± 6 2	365 ± 255
Estradiol	12 8 ± 16 6	8 5 ± 6 2	231 ± 285
Baseline-adjusted estradiol	9 14 ± 14 7	8 5 ± 6 2	161 ± 252
Pharmacokinetic Profiles of Conjugated Estrogens PREMARIN Vaginal Cream 0.5 g			
PK Parameters Arithmetic Mean ± SD	**C_{max} (ng/mL)**	**T_{max} (hr)**	**AUC_{ss} (ng•hr/mL)**
Total estrone	0 60 ± 0 32	6 0 ± 4 0	9 75 ± 4 99
Baseline-adjusted total estrone	0 40 ± 0 28	6 0 ± 4 0	5 79 ± 3 7
Total estradiol	0 04 ± 0 04	7 7 ± 5 9	0 70 ± 0 42
Baseline-adjusted total estradiol	0 04 ± 0 04	7 7 ± 6 0	0 49 ± 0 38
Total equilin	0 12 ± 0 15	6 1 ± 4 7	3 09 ± 1 37

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentration in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone-binding globulin (SHBG) and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is a major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

Estradiol, estrone, and estriol are excreted in the urine, along with glucuronide and sulfate conjugates.

Specific Populations

No pharmacokinetic studies were conducted in specific populations, including patients with renal or hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

14 CLINICAL STUDIES

14.1 Effects on Vulvar and Vaginal Atrophy

A 12-week, prospective, randomized, double-blind placebo-controlled study was conducted to compare the safety and efficacy of 2 PREMARIN Vaginal Cream (PVC) regimens 0.5 g (0.3 mg CE) administered twice weekly and 0.5 g (0.3 mg CE) administered sequentially for 21 days on drug followed by 7 days off drug to matching placebo regimens in the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. The initial 12-week, double-blind, placebo-controlled phase was followed by an open-label phase to assess endometrial safety through week 52. The study randomized 423 generally healthy postmenopausal women between 44 to 77 years of age (mean 57.8 years), who at baseline had ≤ 5 percent superficial cells on a vaginal smear, a vaginal pH ≥ 5.0, and who identified a most bothersome moderate to severe symptom of vulvar and vaginal atrophy. The majority (92.2 percent) of the women were Caucasian (n = 390); 7.8 percent were Other (n = 33). All subjects were assessed for improvement in the mean change from baseline to Week 12 for the co-primary efficacy variables of: most bothersome symptom of vulvar and vaginal atrophy (defined as the moderate to severe symptom that had been identified by the woman as most bothersome to her at baseline); percentage of vaginal superficial cells and percentage of vaginal parabasal cells; and vaginal pH.

In the 12-week, double-blind phase, a statistically significant mean change between baseline and Week 12 in the symptom of dyspareunia was observed for both of the PREMARIN Vaginal Cream regimens (0.5 g twice weekly and 0.5 g daily for 21 days, then 7 days off) compared to matching placebo, see Table 3. Also demonstrated for each PREMARIN Vaginal Cream regimen compared to placebo was a statistically significant increase in the percentage of superficial cells at Week 12 (28 percent and 26 percent, respectively, compared to 3 percent and 1 percent for matching placebo), a statistically significant decrease in parabasal cells (-61 percent and -58 percent, respectively, compared to -21 percent and -7 percent for matching placebo) and statistically significant mean reduction between baseline and Week 12 in vaginal pH (-1.62 and -1.57, respectively, compared to -0.36 and -0.26 for matching placebo).

Endometrial safety was assessed by endometrial biopsy for all randomly assigned subjects at week 52. For the 155 subjects (83 on the 21/7 regimen, 72 on the twice-weekly regimen) completing the 52-week period with complete follow-up and evaluable endometrial biopsies, there were no reports of endometrial hyperplasia or endometrial carcinoma.

Table 3: Mean Change in Most Bothersome Symptom of Dyspareunia Compared to Placebo MITT Population[a]

Dyspareunia*	PVC 0 5 g 2x/wk[b]	Placebo 0 5 g 2x/wk[b]	PVC 0 5 g 21/7[c]	Placebo 0 5 g 21/7[c]
Baseline				
n	52	22	50	18
mean (SD)*	2 43 (0 76)	2 28 (1 04)	2 26 (0 99)	2 32 (0 88)
Week 12				
n	52	21	50	18
mean (SD)*	0 88 (0 96)	1 63 (1 16)	0 77 (1 05)	1 92 (1 03)
Change from Baseline at Week 12				
n	52	21	50	18
LS mean[d] (SD)*	-1 45 (0 16)	-0 69 (0 24)	-1 51 (0 17)	-0 36 (0 26)
P-value vs Placebo	0 01[e]	--	<0 001[f]	--

[a] Women at baseline had ≤5 percent superficial cells on a vaginal smear, a vaginal pH >5 0, and who identified dyspareunia as the most bothersome symptom
[b] PVC 2x/wk = apply PVC twice a week
[c] PVC 21/7 = apply PVC for 21 days and then 7 days of no therapy
[d] Least square mean from ANCOVA adjusting for study site and baseline dyspareunia
[e] Comparison of PVC 2x/wk with placebo 2x/wk
[f] Comparison of PVC 21/7 with placebo 21/7
* Symptom Assessment Scale: 0 (none), 1 (mild), 2 (moderate), 3 (severe)

14.2 Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625 mg)-alone or in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease [(CHD) defined as nonfatal myocardial infarction (MI), silent MI and CHD death], with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other causes. The study did not evaluate the effects of CE or CE plus MPA on menopausal symptoms.

WHI Estrogen-Alone Substudy

The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen alone in predetermined primary endpoints.

Results of the estrogen-alone substudy, which included 10,739 women (average age of 63 years, range 50 to 79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other) after an average follow-up of 7.1 years, are presented in Table 4.

Table 4: Relative and Absolute Risk Seen in the Estrogen-Alone Substudy of WHI

Event	Relative Risk CE vs Placebo (95% nCI[a])	CE n = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-Years	
CHD events[b]	0 95 (0 78–1 16)	54	57
Non-fatal MI[b]	*0.91 (0.73–1.14)*	*40*	*43*
CHD death[b]	*1.01 (0.71–1.43)*	*16*	*16*
All Stroke[b]	1 33 (1 05–1 68)	45	33
Ischemic[b]	*1.55 (1.19–2.01)*	*38*	*25*
Deep vein thrombosis[b,c]	1 47 (1 06–2 06)	23	15
Pulmonary embolism[b]	1 37 (0 90–2 07)	14	10
Invasive breast cancer[b]	0 80 (0 62–1 04)	28	34
Colorectal cancer[d]	1 08 (0 75–1 55)	17	16
Hip fracture[b]	0 65 (0 45–0 94)	12	19
Vertebral fractures[b,c]	0 64 (0 44–0 93)	11	18
Lower arm/wrist fractures[b,c]	0 58 (0 47–0 72)	35	59
Total fractures[b,c]	0 71 (0 64–0 80)	144	197
Death due to other causes[d,e]	1 08 (0 88–1 32)	53	50
Overall mortality[b,c]	1 04 (0 88–1 22)	79	75
Global Index[f]	1 02 (0 92–1 13)	206	201

[a] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons
[b] Results are based on centrally adjudicated data for an average follow-up of 7 1 years
[c] Not included in "global index "
[d] Results are based on an average follow-up of 6 8 years
[e] All deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease
[f] A subset of the events was combined in a "global index" defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone was 12 more strokes while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures.[9] The absolute excess risk of events included in the "global index" was a non-significant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality *[see Boxed Warnings, and Warnings and Precautions (5)]*.

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.

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant difference in distribution of stroke subtype or severity, including fatal strokes, in women receiving CE-alone compared to placebo. Estrogen-alone increased the risk for ischemic stroke, and this excess risk was present in all subgroups of women examined, see Table 4.[10]

Timing of the initiation of estrogen 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 50-59 years of age, a non-significant trend toward reduced risk for CHD *[HR 0.63 (95 percent CI 0.36-1.09)]* and overall mortality *[HR 0.71 (95 percent CI 0.46-1.11)]*.

WHI Estrogen Plus Progestin Substudy

The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years.

For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE plus MPA were 7 more CHD events, 8 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the estrogen plus progestin substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 5. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 5: Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years[a]

Event	Relative Risk CE/MPA vs Placebo (95% nCI[b])	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-Years	
CHD events	1 23 (0 99–1 53)	41	34
Non-fatal MI[b]	*1.28 (1.00–1.63)*	*31*	*25*
CHD death	*1.10 (0.70–1.75)*	*8*	*8*
All Strokes	1 31 (1 03–1 68)	33	25
Ischemic stroke	*1.44 (1.09–1.90)*	*26*	*18*
Deep vein thrombosis[c]	1 95 (1 43–2 67)	26	13
Pulmonary embolism	2 13 (1 45–3 11)	18	8
Invasive breast cancer[d]	1 24 (1 01–1 54)	41	33
Colorectal cancer	0 61 (0 42–0 87)	10	16
Endometrial cancer[c]	0 81 (0 48–1 36)	6	7
Cervical cancer[c]	1 44 (0 47–4 42)	2	1
Hip fracture[b]	0 67 (0 47–0 96)	11	16
Vertebral fractures[c]	0 65 (0 46–0 92)	11	17
Lower arm/wrist fractures[c]	0 71 (0 59–0 85)	44	62
Total fractures[c]	0 76 (0 69–0 83)	152	199
Overall Mortality[e]	1 00 (0 83–1 19)	52	52
Global Index[f]	1 13 (1 02–1 25)	184	165

[a] Results are based on centrally adjudicated data
[b] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons
[c] Not included in "global index "
[d] Includes metastatic and non-metastatic breast cancer, with the exception of *in situ* cancer
[e] All deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease
[f] A subset of the events was combined in a "global index" defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes

Timing of the initiation of estrogen 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 50-59 years of age, a non-significant trend toward reduced risk for overall mortality *[HR 0.69 (95 percent CI 0.44-1.07)]*.

14.3 Women's Health Initiative Memory Study

The estrogen-alone Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age and older (45 percent were 65 to 69 years of age; 36 percent were 70 to 74 years of age; 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed types (having features of both AD and VaD). The most common classification of probable dementia in both the treatment and placebo groups was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.4), and Use in Specific Populations (8.3)]*.

The WHIMS estrogen plus progestin substudy enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were 65 to 69 years of age; 35 percent were 70 to 74 years; 18 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 4 years, the relative risk of probable dementia for CE (0.625 mg) plus MPA (2.5 mg) versus placebo was 2.05 (95 percent CI 1.21-3.48). The absolute risk of probable dementia for CE (0.625 mg) plus MPA (2.5 mg) versus placebo was 45 versus 22 per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease, vascular dementia and mixed types (having features of both AD and VaD). The most common classification of probable dementia in both the treatment and placebo groups was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.4), and Use in Specific Populations (8.5)]*.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.4), and Use in Specific Populations (8.5)]*.

15 REFERENCES

1. Rossouw JE, et al. Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause. *JAMA*. 2007;297:1465-1477.

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16 HOW SUPPLIED/STORAGE AND HANDLING

PREMARIN (conjugated estrogens) Vaginal Cream—Each gram contains 0.625 mg conjugated estrogens, USP.

Combination package Each contains a net wt. 1.5 oz (42.5 g) tube with one plastic applicator calibrated in 0.5 g increments to a maximum of 2 g (NDC 0046-0872-93).

Store at 20 to 25 C (68 to 77 F); excursions permitted to 15 to 30 C (59 to 86 F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See Section 17.5 for FDA-Approved Patient Labeling.

17.1 Vaginal Bleeding

Inform postmenopausal women of the importance of reporting vaginal bleeding to their healthcare provider as soon as possible *[see Warnings and Precautions (5.3)]*

17.2 Possible Serious Adverse Reactions With Estrogens

Inform postmenopausal women of possible serious adverse reactions of estrogen therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia *[see Warnings and Precautions (5.2, 5.3, 5.4)]*.

17.3 Possible Less Serious But Common Adverse Reactions With Estrogens

Inform postmenopausal women of possible less serious but common adverse reactions of estrogen therapy such as headache, breast pain and tenderness, nausea and vomiting.

17.4 Instructions for Use of Applicator

1. Remove cap from tube.

2. Screw nozzle end of applicator onto tube.

3. *Gently* squeeze tube from the *bottom* to force sufficient cream into the barrel to provide the prescribed dose. Use the marked stopping points on the applicator to measure the correct dose, as prescribed by your healthcare provider.

4. Unscrew applicator from tube.

5. Lie on back with knees drawn up. To deliver medication, gently insert applicator deeply into vagina and press plunger downward to its original position.

TO CLEANSE: Pull plunger to remove it from barrel. Wash with mild soap and warm water.

DO NOT BOIL OR USE HOT WATER.

17.5 FDA-Approved Patient Labeling

PREMARIN® (conjugated estrogens) Vaginal Cream

Read this PATIENT INFORMATION before you start using PREMARIN Vaginal Cream and read what you get each time you refill your PREMARIN Vaginal Cream prescription. There may be new information. This information does not take the place of

talking to your healthcare provider about your menopausal symptoms and their treatment.

What is the most important information I should know about PREMARIN Vaginal Cream (an estrogen mixture)?

- Estrogens may increase the chance of getting cancer of the uterus.
- Report any unusual vaginal bleeding right away while you are using PREMARIN Vaginal Cream. 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 the cause.
- Do not use estrogens with or without progestins to prevent heart disease, heart attacks, strokes or dementia.

  Using estrogens, with or without progestins, may increase your chance of getting heart attacks, strokes, breast cancer, and blood clots. Using estrogens, with or without progestins, may increase your chance of getting dementia, based on a study of women age 65 years or older. You and your healthcare provider should talk regularly about whether you still need treatment with PREMARIN Vaginal Cream.

What is PREMARIN Vaginal Cream?

PREMARIN Vaginal Cream is a medicine that contains a mixture of estrogen hormones.

What is PREMARIN Vaginal Cream used for?

PREMARIN Vaginal Cream is used after menopause to:

- **Treat menopausal changes in and around the vagina.** You and your healthcare provider should talk regularly about whether you still need treatment with PREMARIN Vaginal Cream to control these problems.
- **Treat painful intercourse caused by menopausal changes of the vagina.**

Who should not use PREMARIN Vaginal Cream?

Do not start using PREMARIN Vaginal Cream if you:

- **Have unusual vaginal bleeding.**
- **Currently have or have had certain cancers.**

  Estrogens may increase the chance of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should use PREMARIN Vaginal Cream.
- **Had a stroke or heart attack.**
- **Currently have or have had blood clots.**
- **Currently have or have had liver problems.**
- **Are allergic to PREMARIN Vaginal Cream or any of its ingredients.**

  See the list of ingredients in PREMARIN Vaginal Cream at the end of this leaflet.
- **Think you may be pregnant.**

Tell your healthcare provider:

- **If you have any unusual vaginal bleeding.** 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 the cause.
- **About all of your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **About all the medicines you take.** This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how PREMARIN Vaginal Cream works. PREMARIN Vaginal Cream may also affect how your other medicines work.
- **If you are going to have surgery or will be on bedrest.** You may need to stop using PREMARIN Vaginal Cream.
- **If you are breast feeding**. The hormones in PREMARIN Vaginal Cream can pass into your milk.

How should I use PREMARIN Vaginal Cream?

PREMARIN Vaginal Cream is a cream that you place in your vagina with the applicator provided with the cream.

- Take the dose recommended by your healthcare provider and talk to him or her about how well that dose is working for you.
- Estrogens should be used at the lowest dose possible for your treatment only as long as needed. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with PREMARIN Vaginal Cream.

1. Remove cap from tube.
2. Screw nozzle end of applicator onto tube.
3. *Gently* squeeze tube from the *bottom* to force sufficient cream into the barrel to provide the prescribed dose. Use the marked stopping points on the applicator to measure the correct dose, as prescribed by your healthcare provider.
4. Unscrew applicator from tube.
5. Lie on back with knees drawn up. To deliver medication, gently insert applicator deeply into vagina and press plunger downward to its original position.

TO CLEANSE: Pull plunger to remove it from barrel. Wash with mild soap and warm water.

DO NOT BOIL OR USE HOT WATER.

What are the possible side effects of PREMARIN Vaginal Cream?

PREMARIN Vaginal Cream is only used in and around the vagina; however, the risks associated with oral estrogens should be taken into account.

Side effects are grouped by how serious they are and how often they happen when you are treated.

Serious, but less common side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer
- High blood pressure
- Liver problems
- High blood sugar
- Enlargement of benign tumors of the uterus ("fibroids")

Some of the warning signs of these serious side effects include:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting
- Yellowing of the skin, eyes, or nail beds

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptoms that concern you.

Less serious, but common, side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss
- Fluid retention
- Vaginal yeast infection
- Reactions from inserting PREMARIN Vaginal Cream, such as vaginal burning, irritation, and itching

These are not all the possible side effects of PREMARIN Vaginal Cream. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of getting a serious side effect with PREMARIN Vaginal Cream?

- Talk with your healthcare provider regularly about whether you should continue using PREMARIN Vaginal Cream.
- If you have a uterus, talk with your healthcare provider about whether the addition of a progestin is right for you. The addition of a progestin is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus. See your healthcare provider right away if you get vaginal bleeding while using PREMARIN Vaginal Cream.
- Have a pelvic exam, breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease.

General information about the safe and effective use of PREMARIN Vaginal Cream

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use PREMARIN Vaginal Cream for conditions for which it was not prescribed. Do not give PREMARIN Vaginal Cream to other people, even if they have the same symptoms you have. It may harm them. **Keep PREMARIN Vaginal Cream out of the reach of children.**

Latex or rubber condoms, diaphragms and cervical caps may be weakened and fail when they come into contact with PREMARIN Vaginal Cream.

This leaflet provides a summary of the most important information about PREMARIN Vaginal Cream. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about PREMARIN Vaginal Cream that is written for health professionals. You can get more information by calling the toll free number 1-800-934-5556.

What are the ingredients in PREMARIN Vaginal Cream?

PREMARIN Vaginal Cream contains a mixture of conjugated estrogens, which are a mixture of sodium estrone sulfate and sodium equilin sulfate and other components, including sodium sulfate conjugates: 17 α-dihydroequilin, 17 α-estradiol, and 17 β-dihydroequilin. PREMARIN Vaginal Cream also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, benzyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.

PREMARIN (conjugated estrogens) Vaginal Cream—Each gram contains 0.625 mg conjugated estrogens, USP.

Combination package Each contains a net wt. 1.5 oz (42.5 g) tube with one plastic applicator calibrated in 0.5 g increments to a maximum of 2 g (NDC 0046-0872-93).

Store at 20 to 25 C (68 to 77 F); excursions permitted to 15 to 30 C (59 to 86 F) [see USP Controlled Room Temperature].

Wyeth®

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

«TEAR HERE

PATIENT INFORMATION

PREMARIN® (conjugated estrogens) Vaginal Cream

Read this PATIENT INFORMATION before you start using PREMARIN Vaginal Cream and read what you get each time you refill your PREMARIN Vaginal Cream prescription. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms and their treatment.

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- **Had a stroke or heart attack.**

- **Currently have or have had blood clots.**

- **Currently have or have had liver problems.**

- **Are allergic to PREMARIN Vaginal Cream or any of its ingredients.**

  See the list of ingredients in PREMARIN Vaginal Cream at the end of this leaflet.

- **Think you may be pregnant.**

Tell your healthcare provider:

- **If you have any unusual vaginal bleeding.** 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 the cause.

- **About all of your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **About all the medicines you take.** This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how PREMARIN Vaginal Cream works. PREMARIN Vaginal Cream may also affect how your other medicines work.

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PREMARIN (conjugated estrogens) Vaginal Cream—Each gram contains 0.625 mg conjugated estrogens, USP.

Combination package Each contains a net wt. 1.5 oz (42.5 g) tube with one plastic applicator calibrated in 0.5 g increments to a maximum of 2 g (NDC 0046-0872-93).

Store at 20 to 25 C (68 to 77 F); excursions permitted to 15 to 30 C (59 to 86 F) [see USP Controlled Room Temperature].

This product's label may have been updated. For current package insert and further product information, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

Wyeth®

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

(Update W10413C012)
(Update ET01)
Rev Date: November 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20216Orig1s060

DIVISION DIRECTOR REVIEW(S)

Division Director Summary Review for Regulatory Action

Date	November 6, 2008
From	Scott Monroe, MD
Subject	Division Director Summary Review
NDA	NDA 20-216/S-060
Applicant Name	Wyeth Pharmaceuticals, Inc.
Date of Submission	September 4, 2008 (Class 1 resubmission)
PDUFA Goal Date	November 5, 2008
Proprietary Name / Established (USAN) Name	Premarin® Vaginal Cream Conjugated estrogens (CE)
Dosage Forms / Strength	Vaginal cream (b) (4)
Proposed New Indication	Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause
Proposed Regimen	0.5 gram cream (b) (4) intravaginally either (1) twice weekly (e.g., Monday and Thursday) or (2) daily for 21 days followed by 7 days (b) (4)
Action	***Approve (see Section 13.1)***

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers (Original and/or Current Review Cycle)**
Medical Officer Review	Theresa van der Vlugt, MD (primary reviewer)
Statistical Review	Lisa Kammerman, PhD/Mahboob Sobhan, PhD
Pharmacology Toxicology Review	Krishan Raheja, DVM, PhD/Lynnda Reid, PhD
CMC Review/ONDQA	Jean Salemme, PhD/Hasmukh Patel, PhD
Microbiology Review	Not needed
Clinical Pharmacology Review	Doanh Tran, RPh, PhD/Myong-Jin Kim, Pharm.D
DDMAC/SEALD	Iris Masucci, Pharm.D
DSI	Jose Tavarez, MS/Constance Lewin, MD
CDTL Review	Shelley Slaughter, MD, PhD
OSE/DMEPA	Diane Smith, Pharm.D/Todd Bridges, RPh/Denise Toyer, Pharm.D/Carol Holquist, RPh
OSE/DRISK	Nancy Carothers /Jodi Duckhorn, MA

OND	Office of New Drugs
DDMAC	Division of Drug Marketing, Advertising, and Communication
OSE	Office of Surveillance and Epidemiology
DMEPA	Division of Medication Errors Prevention and Analysis
DSI	Division of Scientific Investigations
DRISK	Division of Risk Management
CDTL	Cross-Discipline Team Leader
SEALD	Study Endpoints and Labeling Development Team

1. INTRODUCTION

The objective of NDA 20-216/S-060 is to obtain marketing approval for a new indication and a new doing regimen for Premarin (conjugated estrogens) Vaginal Cream. The proposed new indication is "treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause." The proposed dosing regimen for the new indication is 0.5 gram of Premarin Vaginal Cream (b) (4) intravaginally either (1) twice weekly (e.g., Monday and Thursday) or (2) daily for 21 days followed by 7 days (b) (4) Premarin Vaginal Cream (PVC) has been marketed in the U.S. for more than 25 years and is approved for "the treatment of atrophic vaginitis and kraurosis vulvae." The recommended approved dosing regimen is "0.5 to 2 gram daily, intravaginally, depending on the severity of the condition."

NDA 20-216/S-060 was original submitted in September 2007 and received an Approvable Action on July 25, 2008, because the Division of Reproductive and Urologic Products (DRUP) and the Applicant (Wyeth Pharmaceuticals, Inc) could not reach an agreement on labeling. On September 4, 2008, the Applicant submitted a Class 1 resubmission to DRUP's Action Letter dated July 25, 2008.

In this Memorandum, I will review (1) the major findings and reviewer recommendations from the original review cycle that resulted in the Division's Approvable Letter and (2) the most significant components of the new product labeling, which was found to be acceptable. During the original review cycle, no significant issues regarding the efficacy or safety of PVC for the proposed new indication or the new dosing regimen for PVC were identified.

2. BACKGROUND

2.1 Description of the Product

Premarin (conjugated estrogens) Vaginal Cream contains a mixture of conjugated estrogens, consisting of the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. Premarin is a mixture of sodium estrone sulfate and sodium equilin sulfate, and also contains as concomitant components 17 α-dihydroequilin, 17 α-estradiol, and 17 β-dihydroequilin as sodium sulfate conjugates.

2.2 Recommendations of Primary Medical Reviewer and Cross-Discipline Team Leader (Clinical Team Leader) regarding Approvability

In their original reviews of NDA 20-216/S-060, both the primary Medical Reviewer (Dr. van der Vlugt) and the clinical Team Leader (Dr. Slaughter) recommended approval of PVC for the proposed new indication of "treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause," subject to acceptable product labeling.

Both of the clinical reviewers (Drs. van der Vlugt and Slaughter) and the non-clinical reviewers for Chemistry, Manufacturing, and Controls (CMC), Clinical Pharmacology, and Toxicology found the product labeling for PVC submitted by the Applicant during the current review cycle to be acceptable.

3. CMC RECOMMENDATION

The primary Chemistry Reviewer, Jean Salemme, PhD, made the following statement and recommendations in her review of the original submission signed on March 19, 2008:

> *"For supplement 20-216 / SE2 060, no changes are proposed in the approved chemistry, manufacturing and controls. Additionally, no changes have been made to the chemistry sections of the label.*"

An Environmental Assessment section also was provided in the Application. Based on the information provided, Dr. Salemme determined that *"the request for exclusion from the requirement for an Environmental Assessment is justified."*

Division Director's Comment

- *I concur with the assessment/recommendation made by Dr. Salemme. There are no outstanding CMC issues.*

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

The pharmacology and toxicology of conjugated estrogens are well established. No new non-clinical toxicology studies were submitted in support of NDA 20-216/S-060, and the primary Pharmacology/Toxicology Reviewer, Krishan Raheja DVM, PhD, stated that "*no new clinical studies are required. All have been reviewed under sponsor's original IND 72,606 and approved NDA 20-216 for Premarin Vaginal Cream*." Dr. Raheja also stated the following in his primary review of the original submission signed on March 6, 2008:

> *A. Recommendation on approvability: Nonclinical data support approval.*
>
> *B. Recommendation for nonclinical studies: No new clinical studies are required.*
>
> *C. Recommendations on labeling: Sponsor has proposed acceptable revised labeling in PLR format.*

Division Director's Comment

- *I concur with the conclusions and recommendations of Dr. Raheja.*

5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

The primary Clinical Pharmacology Reviewer, Doanh Tran, PhD, stated the following in his review of the original submission, which he signed on May 16, 2008:

> *"This efficacy supplement does not contain any new clinical pharmacology data. The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds supplemental NDA 20-216 SE 060 acceptable from a Clinical Pharmacology perspective, pending agreements with the Sponsor on labeling."*

6. CLINICAL MICROBIOLOGY

A separate microbiology review was not conducted as the Applicant did not propose any changes in the approved chemistry, manufacturing, and controls (CMC) from those for the currently approved and marketed PVC product.

7. EFFICACY

7.1 Overview of Primary Efficacy and Safety Clinical Trial (Study 071S5-413-NA)

The primary support for the efficacy and safety of PVC for the new indication and new dosing regimen was a single Phase 3 multicenter (49 sites in Canada and the United States), randomized, 4-treatment group, 52-week clinical trial (Study 071S5-413-NA). The trial was double-blind and placebo controlled for the first 12 weeks followed by a 40-week open-label extension.

Treatment Groups. During the double-blind portion of the trial, subjects were randomized to one of 4 treatment groups:

- PVC 0.5 gram [redacted] (b) (4) daily for 21 days, followed by 7 days with no treatment (PVC 21/7, n = 143)
- Placebo cream 0.5 gram daily for 21 days, followed by 7 days with no treatment (Placebo 21/7, n = 72)
- PVC 0.5 gram [redacted] (b) (4) twice weekly (for example, Monday and Thursday) (PVC 2x/wk, n = 140)
- Placebo cream 0.5 gram twice weekly (for example, Monday and Thursday) (Placebo 2x/wk, n = 68)

During the 40-week open-label phase, subjects originally randomized to receive Placebo 21/7 received PVC 21/7. Likewise, subjects originally randomized to receive Placebo 2x/wk received PVC 2x/wk during the extension.

Entry Criteria. Healthy postmenopausal women, 45 to 80 years of age, with an intact uterus and signs and symptoms consistent with moderate to severe vaginal atrophy were potentially eligible for enrollment into the study. Symptoms of vaginal atrophy that qualified for study entry included painful intercourse (dyspareunia), vaginal dryness, vaginal itching, and vaginal burning. Other inclusion criteria included vaginal pH of ≥ 5.0 and vaginal cytology consisting of $\leq 5\%$ superficial cells.

Study Population. A total of 423 subjects were randomized and took study drug. Two hundred eighty-three (283) subjects received PVC (143 received PVC 21/7 and 140 received PVC 2x/wk) during the double-blind phase. One hundred forty (140) subjects received Placebo cream (72 received Placebo 21/7 and 68 received Placebo 2x/wk) during the double-blind phase. During the 40-week open label phase, a total of 394 subjects received PVC (198 subjects received PVC 21/7 and 196 subjects received PVC 2x/wk).

Division Director's Comments

- *DRUP has generally accepted data from a single adequate and well-controlled clinical trial as potentially adequate to support the safety and effectiveness of an estrogen drug product for the indication of treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA).*
- *The data provided in NDA 20-216 are adequate to support the safety and efficacy for the indication of treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.*

7.2 Primary Endpoints and Analyses

7.2.1 Primary Endpoints

For the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause, the Agency's 2003 draft clinical evaluation Guidance Document recommends the following 3 co-primary endpoints:

- Mean change from baseline to Week 12 in vaginal cytology (percentages of superficial and parabasal cells). The primary efficacy analysis should show a statistically significant increase in superficial cells and a statistically significant decrease in parabasal cells.
- Mean change from baseline to Week 12 in vaginal pH. The primary efficacy analysis should show a statistically significant lowering of vaginal pH.
- Mean change from baseline to Week 12 in the moderate to severe self-assessed symptom of VVA identified by the subject as being the most bothersome to her. The primary efficacy analysis should show a statistically significant improvement in the moderate to severe symptom identified by the subject as most bothersome to her at baseline. In this application, symptoms of VVA that were considered for enrollment included painful intercourse (dyspareunia), vaginal dryness, vaginal itching, and vaginal burning. For purpose of analyses, symptoms were assigned values of 0, 1, 2, or 3 for reported severities of none, mild, moderate, and severe, respectively.

7.2.2 Primary Analyses

The Applicant's primary analysis population was a modified intent to treat (mITT) population (n = 423), defined as all randomized subjects who took at least one dose of treatment, had a baseline value, and at least one follow-up visit. The mITT population is smaller for analyses of some of the individual endpoints, depending on whether there is a follow-up visit or not for that endpoint. Dyspareunia is the endpoint most affected, because it could not be assessed if a subject did not have sexual intercourse during the assessment period. Last observation carried forward (LOCF) was used for data for subjects who did not complete 12 weeks. The Clinical Review Team requested during the review that the Applicant also conduct additional analyses for each of the primary endpoints based only on the population of subjects who had all of the following at baseline:

- a vaginal pH ≥ 5
- $\leq 5\%$ superficial cells on vaginal smear
- a most bothersome symptom of VVA with a severity score of 2 or greater

This "revised-mITT population" consisted of 386 subjects. Of these 386 subjects, 290 had sufficient post-baseline data to be included in the most bothersome symptom analysis.
The prespecified analysis was an analysis of covariance (ANCOVA) with treatment group and center as factors and the corresponding baseline value as a covariate. The baseline symptom score was the average score across all scores prior to randomization. For all other variables, the last value recorded prior to randomization was the baseline value.

7.3 Efficacy Findings

7.3.1 Change in Vaginal Cytology

Table 1 lists the mean baseline values and adjusted mean changes from baseline for the percentages of superficial and parabasal cells for each of the 4 treatment groups.

Table 1 Baseline Values and Percent Changes from Baseline for Vaginal Cytology in the mITT Population

Evaluation	Treatment Group			
	PVC 21/7	Placebo 21/7	PVC 2x/wk	Placebo 2x/wk
Superficial Cells				
Number of Subjects	141	71	139	68
Baseline (BL) Mean	0.35%	0.92%	0.76%	0.51%
Adjusted Mean Change from BL at Week 12 (or last visit)	27.9%	3.0%	25.8%	1.0%
p-value versus Placebo	<0.001		<0.001	
Parabasal Cells				
Number of Subjects	141	71	139	68
Baseline (BL) Mean	62.7%	60.6%	59.5%	63.9%
Adjusted Mean Change from BL at Week 12 (or last visit)	-60.6%	-21.5%	-58.2%	-6.6%
p-value versus Placebo	<0.001		<0.001	

Source: Adapted from Tables 7 and 8 of primary Medical Review for NDA 20-216/S-60 (signed July 24, 2008).

Division Director's Comment

- *Compared to the respective placebo treatment group, there was a statistically significant greater increase from baseline in the percentage of superficial cells and a statistically significant greater reduction in the percentage of parabasal cells for both the PVC 21/7 and PVC 2x/wk treatment regimens.*

7.3.2 Change in Vaginal pH

Table 2 lists the mean baseline vaginal pH values and adjusted mean pH changes from baseline for each of the 4 treatment groups.

Table 2 Mean Baseline Values and Changes from Baseline for Vaginal pH in the mITT Population

	Treatment Group			
	PVC 21/7	Placebo 21/7	PVC 2x/wk	Placebo 2x/wk
Number of Subjects	136	68	135	64
Baseline (BL) Mean Vaginal pH	6.72	6.58	6.54	6.67
Adjusted Mean Change from BL at Week 12 (or last visit)	-1.62	-0.36	-1.57	-0.26
p-value vs. placebo	<0.001		<0.001	

Source: Adapted from Table 10 of primary Medical Review for NDA 20-216/S-60 (signed July 24, 2008).

Division Director's Comment

- *Compared to the respective placebo treatment group, there was a statistically significant greater reduction from baseline in vaginal pH for both the PVC 21/7 and PVC 2x/wk treatment regimens.*

7.3.3 Change in Most Bothersome Symptom

Table 3 lists the mean (SE) changes from baseline at Week 12 (or last observation) for each symptom reported as most bothersome at baseline in the revised-mITT population. The revised-mITT population included only those subjects who fully met the protocol-defined inclusion criteria for vaginal pH, vaginal cytology, and a most bothersome moderate to severe symptom of VVA. Among the 4 symptoms of VVA reported as most bothersome at baseline, only the change in dyspareunia at Week 12 (or at the last observation) was statistically significantly greater in the PVC treatment groups compared to that in the respective placebo group (PVC 21/7 group: $p < 0.001$; PVC 2x/wk group: $p = 0.01$).

Table 3 Mean (SE) Changes from Baseline at Week 12 for Each Symptom Reported as Most Bothersome at Baseline in the revised-mITT Population [A]

Symptom	n	PVC 21/7	n	Placebo 21/7	p-value	n	PVC 2x/wk	n	Placebo 2x/wk	p-value
Dyspareunia	50	-1.51 (.17)	18	-0.36 (.26)	<.001	52	-1.45 (.16)	21	-0.69 (.24)	.01
Vaginal Burning	7	-0.22 (.20)	5	-0.64 (.21)	.21	7	-0.64 (.21)	4	-1.39 (.31)	.15
Vaginal Dryness	30	-1.53 (.21)	19	-1.19 (.25)	.29	27	-1.60 (.23)	15	-1.56 (.30)	.91
Vaginal itching	6	-0.87 (.45)	9	-.51 (.41)	.93	12	-0.86 (.32)	8	-1.20 (.48)	.58

[A] Least-squared means based on ANCOVA. Means are adjusted for study site and baseline value. Revised-mITT population includes only those subjects who at baseline had each of a most bothersome moderate to severe symptom of VVA, a vaginal pH ≥ 5.0, and ≤ 5% superficial cells on a vaginal smear.

Source: Table 8 of the FDA Statistical Review for NDA 20-216/S-60 (signed May 27, 2008).

Division Director's Comment

- *These findings support the efficacy of treatment with either PVC 21/7 or PVC 2x/wk to reduce the severity of dyspareunia among healthy post-menopausal women with moderate-to-severe vulvar and vaginal atrophy. Differences between treatment with PVC and placebo were not statistically significant for the other 3 symptoms: vaginal burning, vaginal dryness, and vaginal itching.*

7.3.4 Overall Assessment of Efficacy

The Applicant has demonstrated that both PVC 21/7 and PVC 2x/wk are effective in treating moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to the menopause. Treatment with both dosing regimens of PVC also was effective in reducing vaginal pH, and improving the vaginal cytology profile (i.e., increased the percentage of superficial cells and reduced the percentage of parabasal cells). The change in the vaginal cytology profile and the lowering of vaginal pH are considered to be of secondary clinical benefit.

8. SAFETY FINDINGS

Data from the full 52 weeks of Study 0713S5-413-NA were used to support the safety of PVC 21/7 and PVC 2x/wk. The primary Medical Reviewer thoroughly reviewed and discussed the safety findings from this study as well as the expected risks associated with the use of an estrogen drug product for the management of menopausal symptoms in her original review of this Application. In the following section, only the most important safety findings are summarized.

8.1 Deaths and Other Serious Adverse Events

No deaths were reported during the conduct of Study 0713S5-413-NA.

According to the reviews of the primary Medical Reviewer and the clinical Team Leader, 11 subjects, in total, experienced 13 serious adverse events (SAEs) during the 52-week study (5 during the initial double-blind 12-week period and 6 during the 40-week open label extension). Of the 5 subjects who each reported one serious adverse event during the double-blind phase, 4 subjects were in the PVC 2x/wk treatment group and one subject was in the Placebo 2x/wk treatment group. During the open label Phase, 2 subjects each reported 2 serious adverse events, and 4 subjects each reported one serious adverse event. The reported serious adverse events are listed in Table 4

Table 4 Listing of Reported Serious Adverse Events and Associated Treatment Group

ADVERSE EVENT	TREATMENT GROUP
Double-Blind Phase	
Abdominal pain	PVC 2x/wk
Carcinoma (renal)	PVC 2x/wk
Chest pain	PVC 2x/wk
Intracranial aneurysm	Placebo 2x/wk
Cholecystitis	PVC 2x/wk
Open-Label Phase	
Scleroderma	PVC 2x/wk
Deep vein thrombosis	PVC 21/7
Myocardial infarct	PVC 2x/wk
Gastroenteritis	PVC 21/7
Gastrointestinal disorder	PVC 21/7
Cholelithiasis	PVC 2x/wk
Lung disorder	PVC 2x/wk
Skin carcinoma	PVC 21/7

Each SAE was reported only once.
Source: Modified from Table 17 of primary Medical Review for NDA 20-216/S-60 (signed July 24, 2008).

Division Director's Comment

- *The total number of serious adverse events for a 52-week clinical trial in which 423 subjects were treated with study drug is low. The types of reported serious adverse events in the clinical trial do not raise any new safety concerns for a vaginal estrogen product.*

8.2 Discontinuations for Adverse Events

According to the review of the primary Medical Reviewer and the clinical Team Leader, a total of 26 subjects discontinued from Study 0713S5-413-NA because of adverse events. During the 12-week double-blind portion of the study, 10 of 283 subjects (3.5%) in the PVC treatments groups and 3 of 140 subjects (2.1%) in the placebo groups discontinued from the study because of an adverse event. In the 40-week open label extension, a total of 13 of 394 subjects (3.3%) discontinued from the study because of an adverse event. Among these 394 subjects, 3 of 198 subjects (1.5%) were in the PVC 21/7 group and 10 of 196 subjects (5.1%) were in the PVC 2x/wk group. The adverse events associated with discontinuation from the study in the PVC treatment groups during the double-blind phase of the study were one report each of renal carcinoma, headache, neoplasm (described as a pelvic mass noted after 20 days of treatment), pelvic pain, abdominal distension, nausea, dizziness, rash, vulvovaginal disorder, and vaginitis. The adverse events associated with discontinuation from the study in the PVC treatment groups during the open-label extension phase of the study were one report each of headache, deep vein thrombosis, gastroesophageal reflux, weight gain, leg cramps, anxiety, alopecia, vaginal hemorrhage, vulvovaginal disorder, and 2 reports each of pelvic pain and pruritus.

Division Director's Comment

- *The percentage of subjects discontinuing due to adverse events during the 52-week clinical trial (6.1%) was relatively low for an estrogen product for the treatment of the symptoms of vulvar and vaginal atrophy. Neither the percentage of subjects who discontinued because of an adverse event or the types of adverse events leading to discontinuation raises any new safety concerns.*

8.3 Overall Assessment of Safety

In the Executive Summary of her original review (signed July 24, 2008), the primary Medical Reviewer stated the following:

> *"The safety data presented in the submission demonstrates that the overall safety profile of 0.3 mg (0.5 gram) Premarin® Vaginal Cream, administered either twice weekly continuously (PVC 2x/wk) or daily for 21 days then off for 7 days (PVC 21/7), is acceptable. Both dosing regimens of Premarin® Vaginal Cream were well tolerated."*

In the conclusion of her original review (signed July 25, 2008), the clinical Team Leader stated the following:

> *"The general safety profile and limited endometrial safety profile from Study 0713S5-413-NA, as well as the historical safety profile of the previously approved dosages and regimens of PVC, support the safety of the 0.5 g (0.3 mg conjugated estrogens) PVC regimens; PVC 21 days followed by 7 days of no treatment and PVC 2x/wk continuously."*

I concur with the assessments of both the primary Medical Reviewer and the clinical Team Leader that the safety profile for Premarin Vaginal Cream, administered by either of the proposed dosing regimens, is acceptable for an intravaginal estrogen drug product for the treatment of dyspareunia, a symptom of vulvar vaginal atrophy, due to the menopause. The safety data provided in this Application also are supported by postmarketing safety data from Premarin Vaginal Cream, which has been approved and marketed in the U.S. for more than 25 years for "the treatment of atrophic vaginitis and kraurosis vulvae."

9. ADVISORY COMMITTEE MEETING

This Application was not presented to an Advisory Committee (AC) because the Division did not believe that AC guidance was needed to make a regulatory decision concerning the approvability of the Application.

10. PEDIATRICS

The indication "treatment of dyspareunia, a symptom of vulvar vaginal atrophy, due to menopause" does not apply to adolescents, and therefore a waiver for pediatric studies for this indication was sought. The Pediatric Review Committee (PeRC) concurred with the request, and a waiver for pediatric studies for this indication was granted.

11. OTHER RELEVANT REGULATORY ISSUES

DSI. The Division of Scientific Investigations (DSI) was requested to conduct standard (not-for-cause) inspections at 2 clinical study sites. The DSI summary report included the following:

> "*In general, for the two clinical investigator sites inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. No underreporting of adverse events was noted. Overall, data generated for protocol 0713S5-413-NA at these clinical sites appear acceptable for use in support of NDA 20-216/060…. There were no significant inspectional findings that would adversely impact data acceptability*."

Financial Disclosure Statements. The primary Medical Reviewer made the following statement in her review: "*No data integrity issues are identified in the financial disclosure information provided with the submission*."

Division Director's Comment

- *There are no outstanding regulatory issues that would preclude approval of PVC for the proposed indication of treatment of dyspareunia, a symptom of vulvar vaginal atrophy, due to menopause.*

12. LABELING

The Package Insert (label) for Premarin Vaginal Cream (PVC) was submitted in the format prescribed by the Physician Labeling Rule (PLR). The Package Insert for PVC will be the first approved label for a vaginal estrogen product using the new PLR format. Recommendations regarding labeling were received from the Division of Risk Management (DRISK), Study Endpoints and Label Development (SEALD) Team, Maternal Health Team, and the Division of Medication Errors Prevention and Analysis (DMEPA). All recommendations were considered by DRUP and were incorporated into labeling as deemed appropriate.

The primary Medical Reviewer has described in detail in her labeling review (signed November 6, 2008) the key components of the Package Insert for PVC. Labeling for PVC is based, in part, on class labeling for estrogen and estrogen plus progestin products approved for the treatment of menopausal symptoms.

Major changes from previous labels for estrogen products for the treatment of VVA include:

- (b) (4)
- (b) (4)
- (b) (4)

Additional important information relevant to the safe and effective use of PVC that was retained from previous version of the label includes:

- (b) (4)
- (b) (4)
- (b) (4)

Carton and container labeling was reviewed by DMEPA during the original review cycle for this Application. The labeling reviewed by DMEPA was that for the currently marketed product, which the Applicant wished to retain. Although a search of the FDA's Adverse Event Reporting System (AERS) by DMEPA did not "retrieve any cases of postmarketing confusion with the nomenclature for the product line or the Premarin® Vaginal Cream labels or labeling," DMEPA suggested some changes to the carton labeling to reduce the potential for medication errors. Based on the recommendations from DMEPA, the carton label was revised. Acceptable immediate container and carton labels were submitted on November 4 and 5, 2008, respectively

Final acceptable labeling (Package Insert) for Premarin Vaginal Cream was received from the Applicant on November 6, 2008.

13. DECISION/ACTION/RISK BENEFIT ASSESSMENT

13.1 Regulatory Action

The Applicant has provided sufficient information for me to conclude that Premarin Vaginal Cream, when used in accordance with approved product labeling, will continue to be a safe and effective therapy for the treatment of conditions associated with vulvar and vaginal atrophy due to the menopause. Based on the safety and efficacy data submitted in support of NDA 20-216/S-060 and the agreed to product labeling, Premarin Vaginal Cream will be approved for the new indication of "treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause." The approved dosing regimen for this indication will be 0.5 gram of Premarin Vaginal Cream intravaginally either (1) twice weekly (e.g., Monday and Thursday) or (2) daily for 21 days followed by 7 days (b) (4).

Both the primary Medical Reviewer (Dr. van der Vlugt, in her review signed November 6, 2008) and the clinical Team Leader (Dr. Slaughter, in her concurrence) have recommended approval of Premarin Vaginal Cream for the above indication.

13.2 Risk/Benefit Assessment

The Applicant has demonstrated in a single adequate and well-controlled clinical trial that both proposed dosing regimens for 0.5 gram Premarin Vaginal Cream are safe and effective for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. Both dosing regimens for Premarin Vaginal Cream were statistically superior to placebo in terms of reducing the severity of dyspareunia in postmenopausal women with this complaint secondary to vulvar and vaginal atrophy due to the menopause. The safety profile of each dosing regimen was acceptable. The types, frequency, and severity of adverse events reported in the clinical trial were similar to those associated with the use of approved vaginal estrogen products and do not raise any new concerns that are not already addressed in class labeling for estrogen products. The overall risk/benefit profile for Premarin Vaginal Cream for the treatment of moderate to severe dyspareunia, a symptom of vaginal and vulvar atrophy, due to the menopause, is favorable.

13.3 Recommendation for Postmarketing Risk Management Activities

No postmarketing risk management activities are warranted or requested beyond that of the approved product labeling and routine pharmacovigilance monitoring.

13.4 Recommendation for other Postmarketing Study Commitments

No postmarketing study commitments are warranted or requested.

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/s/

Scott Monroe
11/6/2008 08:26:45 PM
MEDICAL OFFICER

DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS (DRUP)
DIVISION DIRECTOR MEMORANDUM

NDA	NDA 20-216/S-060
Applicant	Wyeth Pharmaceuticals, Inc.
Proprietary Drug Name	Premarin® Vaginal Cream
Established Drug Name	Conjugated estrogens vaginal cream
Drug Class	Estrogen
Indication (Proposed)	Treatment of vulvar vaginal atrophy (VVA), dyspareunia associated with VVA, or kraurosis vulvae
Route of administration	Intravaginal
Dosage Form	Cream
Dosing Regimen	0.5 gram cream (containing 0.3 mg conjugated estrogens) intravaginally either (1) twice weekly (e.g., Monday and Thursday) or (2) daily for 21 days followed by 7 days (b) (4)
CDER Receipt Date	September 25, 2007
PDUFA Goal Date	July 25, 2008
Date of Memorandum	July 25, 2008
Division Director	Scott E. Monroe, MD Division Director, DRUP

1. RECOMMENDATIONS

1.1 Recommendation regarding Approvability

I concur with the primary Medical Reviewer and the clinical Team Leader that 0.5 gram Premarin® Vaginal Cream (containing 0.3 mg conjugated estrogens) is Approvable for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to the menopause. The dosing regimen is 0.5 gram Premarin® Vaginal Cream intravaginally either (1) twice weekly (e.g., Monday and Thursday) or (2) daily for 21 days followed by 7 days (b) (4). Approval is contingent upon the Applicant's submitting acceptable product labeling.

1.2 Basis for Recommendation regarding Approvability

The Applicant has demonstrated in a single adequate and well-controlled clinical trial that both dosing regimens for 0.5 gram Premarin Vaginal Cream are safe and effective for the treatment of moderate to severe dyspareunia associated with vulvar and vaginal atrophy due to the menopause. Both dosing regimens for Premarin Vaginal Cream were statistically superior to placebo in terms of reducing the severity of dyspareunia in postmenopausal women with this complaint secondary to vulvar and vaginal atrophy due to the menopause. The safety profile of

each dosing regimen was acceptable. The types, frequency, and severity of adverse events reported in the clinical trial were similar to those associated with the use of approved vaginal estrogen products and do not raise any new concerns that are not already addressed in class labeling for estrogen products. The overall risk/benefit profile for Premarin Vaginal Cream for the treatment of moderate to severe dyspareunia, a symptom of vaginal and vulvar atrophy due to the menopause, is favorable.

1.3 Recommendation on Risk Management Steps and/or Phase 4 Studies

1.3.1 Recommendation on Risk Management Steps

No postmarketing risk management steps, other than appropriate labeling that clearly delineates the potential risks of estrogen therapy, are required or requested.

1.3.2 Phase 4 Studies

No Phase 4 clinical study commitments are required or requested.

2. PRODUCT DESCRIPTION

Premarin (conjugated estrogens) Vaginal Cream contains a mixture of conjugated estrogens, consisting of the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. Premarin is a mixture of sodium estrone sulfate and sodium equilin sulfate, and also contains as concomitant components 17 α-dihydroequilin, 17 α-estradiol, and 17 β-dihydroequilin as sodium sulfate conjugates. Premarin Vaginal Cream (PVC) has been marketed in the U.S. for more than 25 years and is approved for “the treatment of atrophic vaginitis and kraurosis vulvae.” The recommended approved dosing regimen is “0.5 to 2 gram daily, intravaginally, depending on the severity of the condition.”

3. REVIEW ISSUES

No significant issues regarding the safety or efficacy of PVC, for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to the menopause, were identified during the review of the drug product. No issues regarding the conduct of the primary Phase 3 study or data quality were identified.

4. OVERVIEW OF CLINICAL PROGRAM

In the present NDA supplement, the Applicant has sought approval of a new indication and a new dosing regimen for PVC.

4.1.1 Study 071S5-413-NA

The primary support for the efficacy and safety of PVC for the new indication and new dosing regimen was a single Phase 3 multicenter (49 sites in Canada and the United States), randomized, 4-treatment group, 52-week clinical trial (Study 071S5-413-NA). The trial was double-blind and placebo controlled for the first 12 weeks followed by a 40-week open-label extension.

Treatment Groups. During the double-blind portion of the trial, subjects were randomized to one of 4 treatment groups:

- PVC 0.5 gram (0.3 mg conjugated estrogens) daily for 21 days, followed by 7 days with no treatment (PVC 21/7, n = 143)
- Placebo cream 0.5 gram daily for 21 days, followed by 7 days with no treatment (Placebo 21/7, n = 72)
- PVC 0.5 gram (0.3 mg conjugated estrogens) twice weekly (for example, Monday and Thursday) (PVC 2x/wk, n = 140)
- Placebo cream 0.5 gram twice weekly (for example, Monday and Thursday) (Placebo 2x/wk, n = 68)

During the 40-week open-label phase, subjects originally randomized to receive Placebo 21/7 received PVC 21/7. Likewise, subjects originally randomized to receive Placebo 2x/wk received PVC 2x/wk during the extension.

Entry Criteria. Healthy postmenopausal women, 45 to 80 years of age, with an intact uterus and signs and symptoms consistent with moderate to severe vaginal atrophy were potentially eligible for enrollment into the study. Symptoms of vaginal atrophy that qualified for study entry included painful intercourse (dyspareunia), vaginal dryness, vaginal itching, and vaginal burning. Other inclusion criteria included vaginal pH of ≥ 5.0 and vaginal cytology consisting of $\leq 5\%$ superficial cells.

Study Population. A total of 423 subjects were randomized and took study drug. Two hundred eighty-three (283) subjects received PVC (143 received PVC 21/7 and 140 received PVC 2x/wk) during the double-blind phase. One hundred forty (140) subjects received Placebo cream (72 received Placebo 21/7 and 68 received Placebo 2x/wk) during the double-blind phase. During the 40-week open label phase, a total of 394 subjects received PVC (198 subjects received PVC 21/7 and 196 subjects received PVC 2x/wk).

Division Director's Comments

- *The Division of Reproductive and Urologic Products (DRUP) has generally accepted data from a single adequate and well-controlled clinical trial as potentially adequate to support the safety and effectiveness of an estrogen drug product for the indication of treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA).*
- *The data provided in NDA 20-216 are adequate to support the safety and efficacy for the indication of treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to the menopause.*

4.1.2 Study 0713S5-414-US

A bioavailability study, Study 0713S5-414-US, titled "A Multiple-Dose, Comparative Bioavailability Study of Premarin Vaginal Cream Versus Premarin Oral Tablets in Postmenopausal Women with Atrophic Vaginitis" was conducted to characterize the systemic exposure and bioavailability at steady state of 0.5 gram (0.3 mg conjugated estrogens) of PVC and 0.3 mg Premarin® oral tablets in postmenopausal women with atrophic vaginitis. The study was an open-label, randomized, multiple-dose, 2-treatment, 2-period crossover study conducted in generally healthy postmenopausal women. Each formulation of Premarin was administered

for 7 days: days 1 to 7 (period 1) and days 8 to 14 (period 2). Subjects were randomly assigned to receive either PVC or oral tablets during the first period.

Division Director's Comments

- *The primary Medical Reviewer stated the following in her review: "Study 0713S5-414-US demonstrates that systemic exposure to estradiol and estrone was lower with Premarin® Vaginal Cream than with Premarin® Tablets (mean relative bioavailability was 81% for unconjugated estradiol and 71% for unconjugated estrone)."*
- *This observation suggests that the systemic safety profiles for both dosing regimens of PVC are likely to be at least as good as, and perhaps better than, that associated with the daily use of 0.3 mg Premarin oral tablets, the lowest approved dose for the oral product.*

5. OVERVIEW OF EFFICACY

5.1 Primary Endpoints and Analyses

5.1.1 Primary Endpoints

For the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause, the Agency's 2003 draft clinical evaluation Guidance Document recommends the following 3 co-primary endpoints:

- Mean change from baseline to Week 12 in vaginal cytology (percentages of superficial and parabasal cells). The primary efficacy analysis should show a statistically significant increase in superficial cells and a statistically significant decrease in parabasal cells.
- Mean change from baseline to Week 12 in vaginal pH. The primary efficacy analysis should show a statistically significant lowering of vaginal pH.
- Mean change from baseline to Week 12 in the moderate to severe self-assessed symptom of VVA identified by the subject as being the most bothersome to her. The primary efficacy analysis should show a statistically significant improvement in the moderate to severe symptom identified by the subject as most bothersome to her at baseline. In this application, symptoms of VVA that were considered for enrollment included painful intercourse (dyspareunia), vaginal dryness, vaginal itching, and vaginal burning. For purpose of analyses, symptoms were assigned values of 1, 2, or 3 for reported severities of mild, moderate, and severe, respectively.

5.1.2 Analyses

The Applicant's primary analysis population was a modified intent to treat (MITT) population (n = 423), defined as all randomized subjects who took at least one dose of treatment, had a baseline value, and at least one follow-up visit. The MITT population is smaller for analyses of some of the individual endpoints, depending on whether there is a follow-up visit or not for that endpoint. Dyspareunia is the endpoint most affected, because it could not be assessed if a subject did not have sexual intercourse during the assessment period. Last observation carried forward (LOCF) was used for data for subjects who did not complete 12 weeks. The Clinical Review Team requested during the review that the Applicant also conduct additional analyses for

each of the primary endpoints based only on the population of subjects who had all of the following at baseline:

- a vaginal pH ≥ 5
- $\leq 5\%$ superficial cells on vaginal smear
- a most bothersome symptom of VVA with a severity score of 2 or greater.

This "per protocol population" consisted of 386 subjects. Of these 386 subjects, 290 had sufficient post-baseline data to be included in the most bothersome symptom analysis.

The prespecified analysis was an analysis of covariance (ANCOVA) with treatment group and center as factors and the corresponding baseline value as a covariate. The baseline symptom score was the average score across all scores prior to randomization. For all other variables, the last value recorded prior to randomization was the baseline value.

5.2 Efficacy Findings

5.2.1 Change in Vaginal Cytology

Table 1 lists the mean baseline values and adjusted mean changes from baseline for the percentages of superficial and parabasal cells for each of the 4 treatment groups.

Table 1 Baseline Values and Percent Changes from Baseline for Vaginal Cytology in the MITT Population

Evaluation	Treatment Group			
	PVC 21/7	Placebo 21/7	PVC 2x/wk	Placebo 2x/wk
Superficial Cells				
Number of Subjects	141	71	139	68
Baseline (BL) Mean	0.35%	.92%	0.76%	0.51%
Adjusted Mean Change from BL at Week 12 (or last visit)	27.9%	3.0%	25.8%	1.0%
p-value versus Placebo	<0.001		<0.001	
Parabasal Cells				
Number of Subjects	141	71	139	68
Baseline (BL) Mean	62.7%	60.6%	59.5%	63.9%
Adjusted Mean Change from BL at Week 12 (or last visit)	-60.6%	-21.5%	-58.2%	-6.6%
p-value versus Placebo	<0.001		<0.001	

Source: Adapted from Tables 7 and 8 of primary Medical Review for NDA 20-216/S-60 (signed July 24, 2008).

Division Director's Comment

- *Compared to the respective placebo treatment group, there was a statistically significant greater increase from baseline in the percentage of superficial cells and a statistically significant greater reduction in the percentage of parabasal cells for both the PVC 21/7 and PVC 2x/wk treatment regimens.*

5.2.2 Change in Vaginal pH

Table 2 lists the mean baseline vaginal pH values and adjusted mean pH changes from baseline for each of the 4 treatment groups.

Table 2 Mean Baseline Values and Changes from Baseline for Vaginal pH in the MITT Population

	Treatment Group			
	PVC 21/7	Placebo 21/7	PVC 2x/wk	Placebo 2x/wk
Number of Subjects	136	68	135	64
Baseline (BL) Mean	6.72	6.58	6.54	6.67
Adjusted Mean Change from BL at Week 12 (or last visit)	-1.62	-0.36	-1.57	-0.26
p-value vs. placebo	<0.001		<0.001	

Source: Adapted from Table 10 of primary Medical Review for NDA 20-216/S-60 (signed July 24, 2008).

Division Director's Comment

- *Compared to the respective placebo treatment group, there was a statistically significant greater reduction from baseline in vaginal pH for both the PVC 21/7 and PVC 2x/wk treatment regimens.*

5.2.3 Change in Most Bothersome Symptom

Table 3 lists the mean (SE) changes from baseline at Week 12 (or last observation) for each symptom reported as most bothersome at baseline in the MITT population. Among the 4 symptoms of VVA reported as most bothersome at baseline, only the change in dyspareunia at Week 12 (or at the last observation) was statistically significant (PVC 21/7 group: $p < .001$; PVC 2x/wk group: $p = .002$).

Table 3 Mean (SE) Changes from Baseline at Week 12 for Each Symptom Reported as Most Bothersome at Baseline in the MITT Population [A]

Symptom	n	PVC 21/7	n	Placebo 21/7	p-value	n	PVC 2x/wk	n	Placebo 2x/wk	p-value
Dyspareunia	53	-1.47 (.16)	20	-0.33 (.24)	<.001	54	-1.49 (.15)	23	-0.61 (.23)	.002
Vaginal Burning	9	-0.54 (.43)	5	-0.36 (.48)	.78	9	-0.28 (.38)	5	-1.23 (.71)	.33
Vaginal Dryness	32	-1.46 (.19)	20	-1.24 (.24)	.46	32	-1.52 (.20)	16	-1.43 (.28)	.80
Vaginal itching	7	-0.37 (.43)	11	-0.71 (.37)	.58	12	-0.85 (.34)	9	-1.07 (.47)	.72

[A] Least-squared means based on ANCOVA. Means are adjusted for study site and baseline value.
Source: Table 5 of the FDA Statistical Review for NDA 20-216/S-60 (signed May 27, 2008).

Table 4 lists the mean (SE) changes from baseline at Week 12 (or last observation) for each symptom reported as most bothersome at baseline in the per protocol population. Only the

change in dyspareunia at Week 12 (or at the last observation) was statistically significant (PVC 21/7 group: $p < .001$; PVC 2x/wk group: $p = .01$).

Table 4 Mean (SE) Changes from Baseline at Week 12 for Each Symptom Reported as Most Bothersome at Baseline in the Per Protocol Population [A]

Symptom	n	PVC 21/7	n	Placebo 21/7	p-value	n	PVC 2x/wk	n	Placebo 2x/wk	p-value
Dyspareunia	50	-1.51 (.17)	18	-0.36 (.26)	<.001	52	-1.45 (.16)	21	-0.69 (.24)	.01
Vaginal Burning	7	-0.22 (.20)	5	-0.64 (.21)	.21	7	-0.64 (.21)	4	-1.39 (.31)	.15
Vaginal Dryness	30	-1.53 (.21)	19	-1.19 (.25)	.29	27	-1.60 (.23)	15	-1.56 (.30)	.91
Vaginal itching	6	-0.87 (.45)	9	-.51 (.41)	.93	12	-0.86 (.32)	8	-1.20 (.48)	.58

[A] Least-squared means based on ANCOVA. Means are adjusted for study site and baseline value. Per Protocol population includes only those subjects who at baseline had each of a most bothersome moderate to severe symptom of VVA, a vaginal pH ≥5.0, and ≤5% superficial cells on a vaginal smear.

Source: Table 8 of the FDA Statistical Review for NDA 20-216/S-60 (signed May 27, 2008).

Division Director's Comments

- *These findings support the efficacy of treatment with either PVC 21/7 or PVC 2x/wk to reduce the severity of dyspareunia among healthy post-menopausal women with moderate-to-severe vulvar and vaginal atrophy. These positive results were found both in the overall study population (the MITT population) and in the per protocol population of women who had at baseline (1) a vaginal pH of 5 or greater, (2) no more than 5% superficial cells on a vaginal smear and (3) a reported most bothersome symptom with a severity score of 2 or greater.*
- *Differences between treatment with PVC and placebo were not statistically significant for the other 3 symptoms: vaginal burning, vaginal dryness, and vaginal itching.*

5.3 Overall Assessment of Efficacy

- *The Applicant has demonstrated that both PVC 21/7 and PVC 2x/wk are effective in treating moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to the menopause. Treatment with both dosing regimens of PVC also was effective in reducing vaginal pH, and improving the vaginal cytology profile (i.e., increased the percentage of superficial cells and reduced the percentage of parabasal cells). Both of these latter changes are considered to be of clinical benefit.*

6. SAFETY FINDINGS

Data from the full 52 weeks of Study 0713S5-413-NA were used to support the safety of PVC 21/7 and PVC 2x/wk. The primary Medical Reviewer has thoroughly reviewed and discussed the safety findings from this study as well as the expected risks associated with the use

of an estrogen drug product for the management of menopausal symptoms. In the following section, only the most important safety findings are summarized.

6.1 Deaths and Other Serious Adverse Events

No deaths were reported during the conduct of Study 0713S5-413-NA.

According to the reviews of the primary Medical Reviewer and the clinical Team Leader, 11 subjects, in total, experienced 13 serious adverse events (SAEs) during the 52-week study (5 during the initial double-blind 12-week period and 6 during the 40-week open label extension). Of the 5 subjects who each reported one serious adverse event during the double-blind phase, 4 subjects were in the PVC 2x/wk treatment group and one subject was in the Placebo 2x/wk treatment group. During the open label Phase, 2 subjects each reported 2 serious adverse events, and 4 subjects each reported one serious adverse event. The reported serious adverse events are listed in Table 5.

Table 5 Listing of Reported Serious Adverse Events and Associated Treatment group

ADVERSE EVENT	TREATMENT GROUP
Double-Blind Phase	
Abdominal pain	PVC 2x/wk
Carcinoma (renal)	PVC 2x/wk
Chest pain	PVC 2x/wk
Intracranial aneurysm	Placebo 2x/wk
Cholecystitis	PVC 2x/wk
Open-Label Phase	
Scleroderma	PVC 2x/wk
Deep vein thrombosis	PVC 21/7
Myocardial infarct	PVC 2x/wk
Gastroenteritis	PVC 21/7
Gastrointestinal disorder	PVC 21/7
Cholelithiasis	PVC 2x/wk
Lung disorder	PVC 2x/wk
Skin carcinoma	PVC 21/7

Each SAE was reported only once.
Source: Modified from Table 17 of primary Medical Review for NDA 20-216/S-60 (signed July 24, 2008).

Division Director's Comment

- *The total number of serious adverse events for a 52-week clinical trial in which 423 subjects were treated with study drug is low. The types of reported serious adverse events in the clinical trial do not raise any safety concerns.*

6.2 Discontinuations Due to Adverse Events

According to the review of the primary Medical Reviewer and the clinical Team Leader, a total of 26 subjects discontinued from Study 0713S5-413-NA because of adverse events. During the 12-week double-blind portion of the study, 10 of 283 subjects (3.5%) in the PVC treatments groups and 3 of 140 subjects (2.1%) in the placebo treatment groups discontinued from the study

because of an adverse event. In the 40-week open label extension, a total of 13 of 394 subjects (3.3%) discontinued from the study because of an adverse event. Among these 394 subjects, 3 of 198 subjects (1.5%) were in the PVC 21/7 group and 10 of 196 subjects (5.1%) were in the PVC 2x/wk group. The adverse events associated with discontinuation from the study in the PVC treatment groups during the double-blind phase of the study were one report each of renal carcinoma, headache, neoplasm (described as a pelvic mass noted after 20 days of treatment), pelvic pain, abdominal distension, nausea, dizziness, rash, vulvovaginal disorder, and vaginitis. The adverse events associated with discontinuation from the study in the PVC treatment groups during the open-label extension phase of the study were one report each of headache, deep vein thrombosis, gastroesophageal reflux, weight gain, leg cramps, anxiety, alopecia, vaginal hemorrhage, vulvovaginal disorder, and 2 reports each of pelvic pain and pruritus.

Division Director's Comment

- *The percentage of subjects discontinuing due to adverse events during the 52-week clinical trial (6.1%) was relatively low for an estrogen product for the treatment of the symptoms of vulvar and vaginal atrophy. Neither the percentage of subjects who discontinued because of an adverse event or the types of adverse events leading to discontinuation raise any safety concerns.*

6.3 Endometrial Changes and Endometrial Hyperplasia

One of the more concerning adverse events associated with use of unopposed estrogens in women with a uterus is endometrial hyperplasia or endometrial carcinoma. Endometrial biopsies were to be obtained for subjects at Week 52 (or sooner if clinically indicated or at early termination). For a variety of reasons, end of treatment biopsies were not obtained in almost 40% of subjects. Among the biopsies that were obtained, no cases of endometrial hyperplasia or endometrial carcinoma were reported.

Division Director's Comments

- *Despite the failure to obtain endometrial biopsies from almost 40% of subjects at the end of treatment, the overall endometrial safety data (including results from transvaginal ultrasonography [TVUS] and many years of postmarketing safety data from Premarin Vaginal Cream) were adequate to conclude that the proposed dosing regimens do not raise any safety concerns.*
- *It is important that labeling advise patients and healthcare providers of the need for close clinical surveillance, including adequate diagnostic measures in all cases of postmenopausal vaginal bleeding. The addition of a progestin is generally recommended for women with a uterus to reduce the chance of getting cancer of the uterus.*

6.4 Overall Assessment of Safety Findings

In the Executive Summary of her review, the primary Medical Reviewer stated the following:

> *"The safety data presented in the submission demonstrates that the overall safety profile of 0.3 mg (0.5 gram) Premarin® Vaginal Cream, administered either twice weekly continuously (PVC 2x/wk) or daily for 21 days then off for 7 days (PVC 21/7), is acceptable. Both dosing regimens of Premarin® Vaginal Cream were well tolerated."*

In the conclusion of her review, the clinical Team Leader stated the following:

> *"The general safety profile and limited endometrial safety profile from Study 0713S5-413-NA, as well as the historical safety profile of the previously approved dosages and regimens of PVC, support the safety of the 0.5 g (0.3 mg conjugated estrogens) PVC regimens; PVC 21 days followed by 7 days of no treatment and PVC 2x/wk continuously."*

I concur with the assessments of both the primary Medical Reviewer and the clinical Team Leader that the safety profile for Premarin Vaginal Cream, administered by either of the proposed dosing regimens, is acceptable for an intravaginal estrogen drug product for the treatment of dyspareunia, a symptom of vulvar vaginal atrophy due to the menopause. The safety data provided in this Application are supported by postmarketing safety data from Premarin Vaginal Cream, which has been approved and marketed in the U.S. for more than 25 years for "the treatment of atrophic vaginitis and kraurosis vulvae."

7. RECOMMENDATIONS FROM OTHER DISCIPLINES

There are no unresolved toxicology, CMC (chemistry, manufacturing, or control), or clinical pharmacology issues. No CMC-related changes to the presently approved and marketed drug product were proposed. A request for exclusion from the requirement for an Environmental Assessment was accepted as justified. Premarin® Vaginal Cream is the presently approved tradename.

Recommendations regarding labeling were received from the Division of Risk Management (DRISK), Study Endpoints and Label Development (SEALD) Team, Maternal Health Team, and Division of Medication Error Prevention. All recommendations have been considered by the Division in draft labeling submitted to the Applicant.

8. LABELING

The only outstanding review issue is related to product labeling. Recommendations from the Division regarding revisions to the proposed Package Insert and Patient Package Insert were sent to the Applicant on July 2, 2008. The Applicant has informed the Division that they will not be able to address fully the recommended labeling revisions until after the PDUFA goal date. Label issues will need to be resolved during the next review cycle.

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/s/

Scott Monroe
7/25/2008 04:30:01 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20216Orig1s060

MEDICAL REVIEW(S)

Premarin® Vaginal Cream (estradiol transdermal spray)
Team Leader Review

NDA:	**20216/SE2-060**
Drug:	**Premarin® (conjugated estrogens) Vaginal Cream**
Indications sought:	**"Treatment of vulvar vaginal atrophy (VVA), dyspareunia associated with VVA or kraurosis vulvae"**
Dosage/Form/Route:	**0.5 g (0.3 mg conjugated estrogens) twice weekly (such as Monday and Thursday)** **or** **0.5 g (0.3 mg conjugated estrogens) daily for 21 days then 7days off**
Applicant:	**Wyeth Pharmaceuticals, Inc**. **P.O. Box 8299** **Philadelphia, PA 19101-8299**
Original Submission Receipt Date:	**September 25, 2007**
Primary Review Completion date:	**June 10, 2008**
Date of Final Memorandum:	**July 25, 2008**

Executive Summary:

A single Phase 3, 52-Week trial, Study 0713S5-413-NA, was submitted in support of the efficacy and safety of 0.5 g (0.3 mg conjugated estrogens) Premarin® Vaginal Cream (PVC) daily for 21 days of treatment (PVC 21 days), followed by 7 days of no treatment and 0.5 g (0.3 mg conjugated estrogens) PVC twice weekly (PVC 2x/wk), such as Monday and Thursday, continuously for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy. Results of Study 0713S5-413-NA demonstrated that treatment with either PVC 21 days or PVC 2x/wk continuously, when each was compared to its respective placebo group, yielded statistically significant reductions in the symptoms of dyspareunia (pain with intercourse) in addition to statistically significant reductions in vaginal pH and vaginal parabasal cells and statistically significant increases in vaginal superficial cells by Week 12 of treatment. These improvements in the symptoms and signs of vulvar and vaginal atrophy met the criteria for efficacy as stated in the January 2003 Draft Guidance for Industry, entitled "Estrogen and Estrogen/Progestin Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation" (to be referred to in this review as the Draft HT Clinical Trial Guidance). The Draft HT Clinical Trial Guidance recommends that women who are experiencing moderate to severe symptoms of vulvar and vaginal atrophy should be evaluated in a placebo-controlled clinical trial and that efficacy should be demonstrated with statistically significant improvements when compared to placebo in each of the three co-primary endpoints of vaginal pH, vaginal maturation (increase in superficial cells and decrease in parabasal cells) and the

moderate-to-severe symptom of vaginal atrophy self-identified by the subject as being most bothersome to her.

The safety profile for the two dosage regimens, PVC 21 days or PVC 2x/wk, was consistent with other intravaginal estrogen only products and no concerning signals were seen in the clinical trial.

Based on substantial evidence of efficacy and safety, this reviewer recommends that both regimens, 0.5 g (0.3 mg conjugated estrogens) PVC administered daily for 21 days and 0.5 g (0.3 mg conjugated estrogens) PVC administered twice weekly continuously, be granted the indication of treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to the menopause.

Background and Regulatory History

Premarin® (conjugated estrogens, USP) Cream (NDA 05-900) was marketed in 1946 for vaginal use for the indications of atrophic vaginitis and topical use for acne vulgaris. In 1949, Premarin® Vaginal Cream was developed and labeled for "the treatment of atrophic vaginitis and kraurosis vulvae".

In Federal Register notice (DESI 2238; Docket No. FDC-D-500 [now Docket No. 76N-0261]) published in July 27, 1972 (37 FR 15028), the FDA announced its conclusion that various drug products, including Premarin® Vaginal Cream, were effective in the treatment of atrophic vaginitis and kraurosis vulvae. On October 3, 1972, Ayerst Laboratories, a Division of the American Home Products Corp., now Wyeth Pharmaceutical Inc., filed ANDA 83-273 for Premarin® Vaginal Cream (0.625 mg of conjugated estrogens, USP, per gram of cream). ANDA 83-273 was subsequently approved on October 16, 1978 for the treatment of atrophic vaginitis and kraurosis vulvae. Approved dosages range from 0.5 grams (approximately 0.3 mg of conjugated estrogens) to 2.0 grams (approximately 1.25 mg of conjugated estrogens) applied cyclically (daily for three weeks, then one week off) in a 28-day cycle. In 1991, ANDA 83-273 was renumbered to NDA 20-216 when the Division of Metabolic and Endocrine Products (DMEP) assumed responsibility for Premarin® Vaginal Cream.

An investigational new drug (IND) application for the clinical evaluation of a new dosage regimen for Premarin® Vaginal Cream was submitted to the Division of Reproductive and Urologic Products (DRUP) on June 16, 2005. To date, two studies have been conducted under IND 72,606: Study 0713S5-413-NA, "Efficacy and Safety of 2 Low Dose regimens of Conjugated Estrogen Cream Administered Vaginally in Postmenopausal Women with Atrophic Vaginitis", and Study 0713S5-414-US, "A Multiple-Dose, Comparative Bioavailability Study of Premarin® Vaginal Cream Versus Premarin® Oral Tablets in Postmenopausal Women with Atrophic Vaginitis".

Wyeth Pharmaceuticals did not request a pre-NDA clinical meeting in advance of submission of this supplemental NDA.

NDA 22016/SE2-060 was received by the Agency on September 25, 2007 and administratively filed on, November 24, 2007.

Clinical

Efficacy

Study 0713S5-413-NA

A single Phase 3 trial, Study 0713S5-413-NA, was conducted in support of treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy due to the menopause.

Phase 3b Study 0713S5-413-NA was a multicenter (49 sites in Canada and the United States), randomized 52-week study which was double-blind, parallel group, and placebo-controlled for the first 12 weeks. Seven hundred forty two (742) healthy postmenopausal subjects (each woman was required to have an intact uterus) were screened to select those who had signs and symptoms consistent with moderate to severe vaginal atrophy, defined as:

a. baseline composite score (at initial screening visit) of at least 5 (1 = mild, 2 = moderate, 3 = severe) for the symptoms of vaginal dryness, itching/burning, and dyspareunia (pain during intercourse),
b. total score of ≤ 15 on the Genital Health Clinical Evaluation (GHCE) instrument,
c. vaginal pH of ≥ 5.0.

Four-hundred thirty one (431) subjects were randomly assigned to 1 of 4 treatment groups (2 active groups and 2 matching placebo groups). Subjects received a 100 day supply of study medication at the time of randomization. Eight (8) subjects did not take any medications and never returned to clinic. The remaining 423 subjects were analyzed by the statistical team as a modified intent-to-treat (mITT) population, defined as all randomized subjects who took at least one dose of treatment, had a baseline value and at least one follow-up visit.

During the 12-week double-blind phase of the study, subjects were to return at Weeks 4, 6, and 12 for safety and efficacy assessments. In the double-blind period, the treatment interval began on the date on which the subject was randomly assigned to a treatment group and continued through the week 12 visit date or the termination date for subjects withdrawing before week 12.

The 12-week double-blind portion of Study 0713S5-413-NA was followed by a 40-week open-label period. During the 40-week open-label portion, all subjects, including those randomly assigned to placebo treatment groups received PVC treatment. Thus, subject initially randomized to placebo received PVC during the 40-week open-label period.

Study medication for the open-label period included: graduated applicators for vaginal administration and PVC in 42.5 gram tubes (commercial package). On day 84, at the start of the open-label period, each subject received a sufficient number of 42.5 gram tubes to last approximately 100 days. On day 182, each subject was given a sufficient number of 42.5 gram tubes for the last 6 months of the study.

For the entire study, data were collected through the week 52 visit date or the termination date for subjects withdrawing before week 52

Demographics
A healthy postmenopausal woman age 45 to 80 years of age was to be enrolled if she had an intact uterus and signs and symptoms consistent with moderate to severe vaginal atrophy.

The mean ages (± SD) per treatment groups were 57.68 ± 5.79, 57.96 ± 5.76, 57.47 ± 5.45 and 58.69 ± 5.68 in the PVC 21 day, placebo 21 day, and PVC 2x/wk, and placebo 2x/wk, respectively. The subjects were mostly Caucasian; approximately 92.2% (390/423). No racial description was given for the remaining 7.8%. The mean weight in kg was 68.28± 13.56. There were no statistically significant differences among treatment groups for any of the described demographic characteristics.

VVA

A total of 431 subjects were randomized in a 2:1 PVC:placebo ratio as follows:

- 0.5 g (0.3 mg conjugated estrogens) PVC daily for 21 days of treatment, followed by 7days of no treatment (PVC 21 days) – n=145
- 0.5 g placebo cream for 21 days of treatment, followed by 7 days of no treatment – n=72
- 0.5 g (0.3 mg conjugated estrogens) PVC twice weekly (PVC 2 x/wk), such as Monday and Thursday, continuously – n=141
- 0.5 g placebo twice weekly, such as Monday and Thursday, continuously – n=73

Symptoms of VVA
Vaginal symptoms were assessed daily using diary cards beginning in the screening period. Symptoms assessed included vaginal dryness, itching, burning, and dyspareunia. Subjects were to score each of these symptoms daily based on the scoring system of: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 5 = not applicable and 9 = not done. The subject self-identified her most bothersome symptom at screening.

Among 412 subjects who reported a most bothersome symptom at baseline, the most common complaint was dyspareunia (painful intercourse), followed by vaginal dryness. Vaginal itching and vaginal burning were less commonly reported by subjects at baseline.

Four-hundred twenty three (423) subjects were analyzed by the statistical team as a modified intent-to-treat (mITT), defined as all randomized subjects who took at least one dose of treatment, had a baseline value and at least one follow-up visit. Three-hundred ninety four (394) subjects completed the 12-week double-blind part of the study. The pre-specified analysis was an analysis of covariance with treatment group and center as factors and the corresponding baseline value as a covariant. The last observation carried forward was used for subjects who did not complete 12-weeks.

The mITT analyses (as defined by the Agency's Statistical Review Team) are shown in Table 1 (from the Statistical Review Table 5).

Table 1. Adjusted Mean Change from Baseline[a] (with standard errors) by Each Symptom Noted as Most Bothersome at Baseline for All Subjects Who Took at Least One Dose of Treatment, Had a Baseline Value and at Least One Follow-Up Visit, LOCF.

Symptoms	**PVC 21 days**	**Placebo 21 days**	**PVC 2 x/wk**	**Placebo 2x/wk**
Dyspareunia				
n	53	20	54	23
adjusted mean change (SE)	-1.47 (0.16)	-0.33 (24)	-1.49 (0.15)	-0.61 (0.23)
p[b]	<0.001		0.002	
Vaginal Dryness				
n	32	20	32	16
adjusted mean change (SE)	-1.46 (0.19)	-1.24 (0.24)	-1.52 (0.20)	-1.43 (0.28)
p	0.46		0.8	
Vaginal Burning				
n	9	5	9	5
adjusted mean change (SE)	-0.54 (0.43)	-0.36 (0.48)	-0.28 (0.38)	-1.23 (0.71)
p	0.78		0.33	
Vaginal Itching				
n	7	11	12	9
adjusted mean change (SE)	-0.37 (0.43)	-0.71 (0.37)	-0.85 (0.34)	-1.07 (0.47)
p	0.58		0.72	

Abbreviations: LOCF = last observation carried forward; SE = standard error.
[a]ANCOVA – means are adjusted for baseline and study site
[b] statistical significance declared p <0.002

In the above mITT analyses, both active treatment groups, 0.5 g PVC delivered for 21 days (PVC 21 days) and delivered twice weekly (PVC 2x/wk), when each was compared to its respective placebo group, were shown to be statistically significantly different for the symptom of dyspareunia. No statistically significant difference between active treatment groups and placebo were shown for the symptoms of vaginal dryness, vaginal burning and vaginal itching.

The Draft HT Clinical Trial Guidance recommends that for the indication of treatment of moderate to severe symptoms of vulvar and vaginal atrophy, study participants be enrolled who have self-identified at least one moderate to severe symptom that is the most bothersome to her, have no greater than 5 percent superficial cells on a vaginal smear, and have a vaginal pH > 5.0. Further, the primary efficacy analyses for a trial of vulvar and vaginal atrophy should demonstrate statistically significant improvement

versus placebo from baseline to week 12 of treatment in all of the following co-primary parameters:

1. Decrease of parabasal vaginal cells and
2. Increase in superficial vaginal cells)
3. Lowering of the vaginal pH
4. Decrease in the severity of the moderate to severe symptom identified by the subject as being most bothersome to her

On November 15, 2007, the Agency requested, in an electronic mail communication, that the applicant provide:

1. "The number of subjects in each treatment group who, at baseline, met all the 3 co-primary endpoints" (i.e. enrollment criteria for the co-primary endpoints):
    1. Identified at least 1 moderate to severe vulvar and vaginal atrophy symptom that was also self-identified as most bothersome.
    2. A vaginal pH of ≥ 5.0.
    3. No more than 5% superficial cells on a vaginal smear.
2. "The mean change (SD) between baseline and week 12 for each individual moderate to severe symptom identified as most bothersome for each treatment group for subjects who at baseline met the criteria as specified in #1 for most bothersome symptom, vaginal pH and superficial vaginal cells."
3. "The p-value (active treatment versus placebo) at week 12 for each individual symptom as delineated in #2."

On December 13, 2007, Wyeth provided the information requested in two tables (sNDA 20-216/SE2-060 query response December 13, 2007 - Tables 1-1 and 1-2). These tables were used to construct Tables 2 and 3 as follows in this review (see also Medical Officer Review Tables 14 and 15 and Statistical Review Table 7). The same information was also included in the 4-Month Safety Update (Table 9-9).

Table 2 was submitted to respond to the Agency's query to provide the number of subjects in each treatment group who, at baseline, met all three baseline criteria.

Table 2. Summary Tabulation of Mean Weekly Symptom Change Score, at Week 12: MITT Population of Most Bothersome, LOCF

	PVC 21 days (n = 93)[a]		**Placebo 21 days** (n = 51)[a]		**PVC 2x/wk** (n = 98)[a]		**Placebo 2x/wk** (n = 48)[a]	
Symptom	n[b]	Mean (SD)	n[b]	Mean (SD)	n[b]	Mean (SD)	n[b]	Mean (SD)
Dyspareunia	50	-1.48 (1.17)	18	-0.40 (1.01)	52	-1.55 (0.92)	21	-0.62 (1.23)
Vaginal dryness	30	-1.31 (1.06)	19	-1.28 (1.21)	27	-1.40 (0.98)	15	-1.26 (1.08)
Vaginal burning	7	-0.54 (0.99)	5	-0.27 (0.93)	7	-1.23 (1.34)	4	-0.66 (1.68)
Vaginal itching	6	-0.63 (0.96)	9	-0.69 (0.76)	12	-0.99 (1.09)	8	-0.29 (0.84)

Abbreviations: LOCF = last observation carried forward; MITT = modified intent –to-treat; and SD = standard deviation.

[a.] Per the Applicant, the total number of subjects equals the sum of subjects meeting each of the 4 symptoms because each subject has only 1 most bothersome symptom.

[b] n = number of subjects satisfying all 3 inclusion criteria (identified at least 1 moderate to severe vulvar and vaginal atrophy symptom that was also self-identified as most bothersome, a vaginal pH of ≥ 5.0 and no more than 5% superficial cells on a vaginal smear).

Table 3 was submitted in response to the Agency's query 2 and 3 on the mean change (SD) between baseline and Week 12 for each individual moderate to severe symptom identifies as most bothersome and the p-value for each treatment compared to placebo

Table 3: Summary Tabulation of ANCOVA[a] for the Mean Change (SE), Baseline to Week 12, for Each Individual Moderate to Severe Symptom Identified as Most Bothersome: MITT Population, LOCF

Symptom	Adjusted Mean (SE)			Adjusted Mean (SE)		
	PVC 21 days (n = 93)[b]	**Placebo 21 days** (n = 51)[b]	p-Value[b]	**PVC 2x/wk** (n = 98)[b]	**Placebo 2x/wk** (n = 48)[b]	p-Value[c]
Dyspareunia	-1.52 (0.13)	-0.41 (0.22)	<.001	-1.49 (0.13)	-0.66 (0.21)	0.001
Vaginal dryness	-1.48 (0.17)	-1.11 (0.22)	0.189	-1.39 (0.18)	-1.16 (0.24)	0.441
Vaginal burning	-0.92 (0.40)	-0.23 (0.45)	0.276	-0.91 (0.40)	-0.60 (0.51)	0.633
Vaginal itching	-0.61 (0.38)	-0.59 (0.31)	0.975	-0.99 (0.27)	-0.42 (0.34)	0.196

Abbreviations: LOCF = last observation carried forward; n = number of subjects satisfying all 3 inclusion criteria (identified at least 1 moderate to severe vulvar and vaginal atrophy symptom that was also self-identified as most bothersome, a vaginal pH of ≥ 5.0 and no more than 5% superficial cells on a vaginal smear); SE = standard error; and ANCOVA = Analysis of covariance.

[a.] ANCOVA with baseline value as the covariate

[b]Per the Applicant, the total number of subjects equals the sum of subjects meeting each of the 4 symptoms because each subject has only 1 most bothersome symptom.

In the Applicant's ANCOVA (with baseline as covariant) for the mean change in the individual symptoms from baseline to Week 12 for subjects meeting all three enrollment criteria, each PVC treatment group when compared to its respective placebo group demonstrated a statistically significant reduction in the severity of the symptom of dyspareunia. No statistically significant difference between active treatment groups and placebo were shown for the symptoms of vaginal dryness, vaginal burning and vaginal itching.

The Statistical Reviewer confirmed that the data presented in Tables 2 and 3 were unadjusted for study site as was specified in the original statistical analysis plan. The Statistical Reviewer re-analyzed the data and adjusted the means for both study site and baseline value. The results of the ANCOVA (with standard error) with baseline and study site as covariate of the change from baseline at week 12 by each symptom reported as most bothersome symptom at baseline among the subgroup of subjects who had a baseline vaginal pH of ≥ 5.0, who had ≤ 5% superficial cells on a vaginal smear and whose most bothersome symptom was moderate to severe are shown in Table 4.

Table 4. Adjusted Mean Change from Baseline (with standard errors) by Each Symptom Noted as Most Bothersome at Baseline for All Subjects Who Had at the Baseline Determination, a Vaginal pH of 5 or Greater, ≤ 5% Vaginal Superficial Cells and at Least One Symptom That Was Self-Identified as Most Bothersome, LOCF.

Symptom	**PVC 21 days** (n = 93)	**Placebo 21 days** (n = 51)	**PVC 2x/wk** (n = 98)	**Placebo 2x/wk** (n = 48)
Dyspareunia				
n[a]	50	18	52	21
adjusted mean change[b] (SE)	-1.51 (0.17)	-0.36 (0.26)	-1.45 (0.16)	-0.69 (0.24)
p[c]	<0.001		0.01	
Vaginal Dryness				
n[a]	30	19	27	15
adjusted mean change[b] (SE)	-1.53 (0.21)	-1.19 (0.25)	-1.60 (0.23)	-1.56 (0.30)
p	0.29		0.91	
Vaginal Burning				
n[a]	7	5	7	4
adjusted mean change[b] (SE)	-0.22 (0.20)	-0.64 (0.21)	-0.64 (0.21)	-1.39 (0.31)
p	0.21		0.15	
Vaginal Itching				
n[a]	6	9	12	8
adjusted mean change[b] (SE)	-0.87 (0.45)	-0.51 (0.41)	-0.86 (0.32)	-1.20 (0.48)
p	0.93		0.58	

[a] n = number of subjects satisfying all 3 inclusion criteria (identified at least 1 moderate to severe vulvar and vaginal atrophy symptom that was also self-identified as most bothersome, a vaginal pH of ≥ 5.0 and no more than 5% superficial cells on a vaginal smear)

[b.] ANCOVA – means are adjusted for baseline and study site

[c] Statistical Significance declared p <0.002

In the ANCOVA, with baseline and site as covariants, of the subset of subjects meeting the enrollment criteria at baseline as recommended by the Draft HT Clinical Trial guidance, the symptom of dyspareunia is the only symptom with a statistically significant difference in the mean change of severity from baseline to Week 12 for each active treatment groups, PVC 21/7 and PVC 2x/wk, when compared to its respective placebo ($p<0.001$ and $p=0.01$, respectively).

Vaginal pH

The NDA submission reported the mITT (all randomized subjects who took at least one dose of treatment, had a baseline value and at least one follow-up visit) analysis of vaginal pH. Statistical significance ($p< 0.001$) for the change from baseline to Week 12 was reported for each active treatment group, PVC 21 days and PVC 2x/wk continuously, compared to the appropriate placebo.

On May 21, 2008, the Agency requested that Wyeth provide analyses of the vaginal pH, vaginal superficial cell and vaginal parabasal cells for the population of subjects meeting the following Draft HT Clinical Trial Guidance recommended criteria at baseline:

1. Identified at least 1 moderate to severe vulvar and vaginal atrophy symptom that was also self-identified as most bothersome.
2. A vaginal pH of ≥ 5.0.
3. No more than 5% superficial cells on a vaginal smear.

These analyses, presented in Table 5 and Table 6 of this review, had not been previously provided in the original submission or subsequent responses.

The analysis of mean change in vaginal pH at Week 12 for subjects meeting the baseline enrollment criteria for a VVA study is shown in Table 5.

Table 5. Mean Change in Vaginal pH at Week 12 for All Subjects Meeting the Enrollment Criteria for Symptoms, pH and Vaginal Superficial cells, LOCF

	PVC 21 days	**Placebo 21 days**	**PVC 2 x/wk**	**Placebo 2x/wk**
Vaginal pH				
n[a]	91	48	96	47
Baseline Mean (SD)	6.71 (0.72)	6.50 (0.70)	6.50 (0.79)	6.69 (0.81)
Adj. Mean Change from Baseline (SE)	-1.55 (0.09)	-0.49 (0.12)	-1.63 (0.09)	-0.24 (0.12)
p-value vs. placebo	<0.001		<0.001	

Abbreviations: LOCF = last observation carried forward.

[a]n = number of subjects satisfying all 3 inclusion criteria (identified at least 1 moderate to severe vulvar and vaginal atrophy symptom that was also self-identified as most bothersome, a vaginal pH of ≥ 5.0 and no more than 5% superficial cells on a vaginal smear)

Relative to its respective placebo group, each PVC group shows a statistically significant decrease from baseline in the vaginal pH measured at Week 12. It is not clear from the Applicant's description of the analysis, that an ANCOVA with adjustment for both baseline and site was utilized for the data. However, based on analogy to the symptom data, it is unlikely that if only the covariant of baseline was used by the Sponsor for their analysis that the outcome would change with respect to statistical significance when considering both covariants of baseline and study site.

Vaginal superficial and parabasal cells

The Applicant's analyses of mean change in vaginal superficial and parabasal cells at Week 12 for subjects meeting the baseline enrollment criteria for a VVA study are shown in Table 6.

Table 6. Mean Change in Vaginal Superficial and Parabasal Cells at Week 12 for All Subjects Meeting the Enrollment Criteria for Symptoms, pH and Vaginal Superficial cells[a], LOCF

Vaginal Lateral Wall Cytology	**PVC 21 days**	**Placebo 21 days**	**PVC 2x/wk**	**Placebo 2x/wk**
Superficial Cells				
n[a]	92	50	98	48
Baseline Mean Percentage (S.D.)	0.33 (1.24)	0.70 (1.75)	0.20 (0.99)	0.42 (1.40)
Adjusted Mean Change in Percentage at Week 12 (S.E.)	23.68 (2.03)	4.69 (2.73)	28.35 (1.98)	1.20 (2.83)
p-value vs. placebo	<0. 001		<0. 001	
Parabasal Cells				
n	92	50	98	48
Baseline Mean Percentage (S.D.)	63.80 (44.1)	56.5 (43.5)	60.2 (45.1)	61.5 (43.5)
Adjusted Mean Change in Percentage at Week 12 (S.E.)	-61.72 (2.76)	-21.73 (3.69)	-58.41 (2.61)	-8.93 (3.85)
p-value vs. placebo	<0. 001		<0. 001	

Abbreviations: LOCF = last observation carried forward.
[a]n = number of subjects satisfying all 3 inclusion criteria (identified at least 1 moderate to severe vulvar and vaginal atrophy symptom that was also self-identified as most bothersome, a vaginal pH of ≥ 5.0 and no more than 5% superficial cells on a vaginal smear)

Relative to its respective placebo group, each PVC group shows a statistically significant decrease from baseline in vaginal parabasal cells and a statistically significant increase in vaginal superficial cells as determined at Week 12. It is not clear from the Applicant's description of the analyses, that ANCOVA determinations with adjustment for both baseline and site were utilized for the data. However, based on analogy to the symptom data, it is unlikely that if only the covariant of baseline was used by the Sponsor for their analysis that the outcome would change with respect to statistical significance when considering both covariants of baseline and study site.

Safety

Data from the full 52 weeks of Study 0713S5-413-NA was used to support the safety of PVC 21 days and PVC 2x/wk.

Endometrial hyperplasia

One of the most concerning adverse events most commonly associated with use of unopposed estrogens in women with a uterus is endometrial hyperplasia. Endometrial biopsies were required for all randomly assigned subjects at week 52 (or sooner if clinically indicated or at early termination). A total of 423 subjects (215 treated with PVC 21 days at some point during the 52-week study and 208 subjects treated with PV 2x/wk at some point during the 52-week study) were followed up and should have had their endometrium sampled for histology.

Table 7 (derived from information in the Medical Officer Review) provides the endometrial histology results from the reported endometrial biopsies.

Table 7: Endometrial Histology Results from Biopsies Obtained at End-of- Study 0713S5-413-NA (Week 52 or for cause or early termination).

	PVC 21 days n	**PVC 2x/wk n**
Endometrial Biopsy Result		
No endometrial tissue	39	63
Scant endometrial tissue, no hyperplasia or cancer	55	45
Normal	24	22
Proliferative	6	6
Not done	92	74

The endometrial histology results, as reported by the Application, were not categorized with a high level of discrimination. The Draft HT Clinical Trial Guidance recommends the following basic endometrial histology categorization: 0. - No tissue; 1. - Tissue insufficient for diagnosis; 2. – Atrophic; 3. – Inactive; 4. – Proliferative (a. weakly proliferative, b. active proliferative and c. disordered proliferative); 5. – Secretory [a. cyclic type and b. progestational type (including stromal decidualization)]; 6. - Menstrual type; 7. - Simple hyperplasia without atypia; 8. - Simple hyperplasia with atypia; 9. - Complex hyperplasia without atypia; 10. - Complex hyperplasia with atypia; and 11. - Carcinoma (specify type). The categorization of endometrial specimens from Study 0713S5-413-NA, as provided by the Applicant, was vague and minimally informative. Further, a high percentage (39.2 %, 166 of 423) of subjects did not have endometrial biopsies at study end as presumably required by the study protocol. This percentage is close to double that usually seen in 52 week trials. This reviewer believes that the Sponsor did not ensure that the study investigators followed through on the study requirement for endometrial biopsy. Despite these very obvious shortcomings of the endometrial biopsy assessment at 52 weeks, no cases of endometrial cancer or complex or simple endometrial hyperplasia were reported. There appear to be no alarming findings in this report of the endometrial histology in Study 0713S5-413-NA.

Other Serious Adverse Events

No deaths occurred during the conduct of primary, Phase 3 Study 0713S5-413-NA.

In total, 11 subjects experienced 13 serious adverse events (SAES) during the total 52 weeks of study (5 during the double blind initial 12 weeks and 6 during the 40 week open label extension). Of the 5 subjects who experienced SAEs during the double-blind phase of Study 0713S5-413-NA, 4 subjects were in the PVC 2x/wk treatment group and 1 subject was in the placebo 2x/wk treatment group.

The most common adverse events across all treatment groups in both phases of the study were in the body as a whole system (abdominal pain, headache and pelvic pain). Vaginitis was also commonly reported during the open-label phase of the trial.

The percentage of subjects discontinuing due to adverse events was small (approximately 3 percent in each phases of the study) and did not raise a safety concern. The incidence of discontinuations due to adverse events during the open-label phase, was also similar between the PVC vs. placebo treatment groups (3.1%, 8 of 261 subjects in the two original PVC treatment groups versus 3.7%, 4 of 133 subjects in the two original matching placebo treatment groups who received PVC during the open-label phase). Subjects in the PVC 21 day group reported more discontinuations during both phases of the studies than did the PVC 2x/wk group. Discontinuations during the 12 week double blind phase were due to headache, pelvic pain, abdominal pain, rash and vaginitis. Discontinuations during the open-label phase were due to pruritis, deep vein thrombosis, vaginal hemorrhage, vulvovaginal disorder, headache and pelvic pain.

All 423 subjects in the safety population were followed up after their last visit, whether they discontinued participation in the study or completed the study.

Division of Scientific Investigation (DSI)

The following two centers were recommended for audits by DSI:

1. Center 017
   Investigator – Dr. Barry Lubin
   Hampton Rhodes Center for Clinical Research, Inc.
   Norfolk, VA

2. Center 037
   Investigator – Dr. Celine Bouchard
   Clinique RSF, Inc.
   Quebec, Canada

For each Center 017 and 037, the DSI auditors concluded that the "data generated for protocol 0713S5-413-NA at this clinical site appear acceptable for use in support of NDA 20-216/060."

Office of Clinical Pharmacology (OCP)

The efficacy supplement does not contain any new clinical pharmacology data. (b) (4)

The OCP/Division of Clinical Pharmacology 3 finds supplemental NDA 20-216 to be acceptable from a Clinical Pharmacology perspective, pending agreements with the Sponsor on labeling.

Pre-Clinical Pharmacology and Toxicology

Nonclinical studies were reviewed under IND 72,606 and supported approval under NDA 20-216. That nonclinical data supports approval of this supplemental NDA.

From the Preclinical Pharmacology and Toxicology perspective, the labeling is acceptable and approval is recommended.

Chemistry, Manufacturing and Controls (CMC):

No changes to the approved CMC are proposed in this supplement. Additionally no changes have been made to the chemistry sections of the label. A request for exclusion from the requirement for an Environmental Assessment was accepted as justified.

From a CMC perspective the application can be approved.

Microbiology:

Study 0713S5-413-NA used drug product manufactured with the approved chemistry, manufacturing and controls. Per the CMC reviewer, no clinical microbiology consult was needed or requested for NDA 20-216/SE2-060.

Product Name

Premarin® Vaginal Cream is the previously approved proprietary name.

Conclusions and Recommendations

Study 0713S5-413-NA provided evidence that treatment with each of the 0.5 g (0.3 mg conjugated estrogens) PVC regimens, PVC 21days followed by 7 days of no treatment or PVC 2x/wk continuously, when compared to treatment with matching placebo resulted in statistically significant improvement in the severity of the most bothersome moderate to severe symptom of dyspareunia (pain with intercourse) in addition to the statistically significant improvements in vaginal superficial cells (increased) and parabasal cells (decreased) and vaginal pH (decreased). These improvements in the symptoms and signs of vulvar and vaginal atrophy met the criteria for efficacy as stated in the January 2003 Draft HT Clinical Trial Guidance.

The 0.5 g (0.3 mg conjugated estrogens) PVC drug product is the first vaginally administered drug product to successfully demonstrate treatment of a moderate to severe symptom of VVA. One concern for approval of a previous orally administered product was that it had not shown superiority to a vaginal placebo lubricant. In demonstrating superiority to a vaginal placebo (glyceryl monostearate, cetyl esters wax, cetyl alcohol, methyl stearate, glycerin, white wax, propylene glycol monostearate, benzyl alcohol, sodium lauryl sulfate, mineral oil - (b) (4)), which could be considered as a vaginal lubricant, (b) (4)) as stated in the January 2003 Draft Guidance for Industry, entitled "Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Prescribing Information for Health Care Providers and Patient Labeling."

The general safety profile and limited endometrial safety profile from Study 0713S5-413-NA, as well as the historical safety profile of the previously approved dosages and regimen of PVC, support the safety of the 0.5 g (0.3 mg conjugated estrogens) PVC regimens; PVC 21days followed by 7 days of no treatment and PVC 2x/wk continuously.

This reviewer concurs with the primary clinical and non-clinical review disciplines and I recommend that once labeling negotiations with the Sponsor have been successfully completed with a final agreed upon label, the 0.5 g (0.3 mg conjugated estrogens) PVC regimens, PVC 21days followed by 7 days of no treatment and PVC 2x/wk continuously, receive approval for the indication of treatment of moderate to severe dyspareunia (pain with intercourse), symptom of vaginal atrophy, due to the menopause.

The main review issues in dispute for this supplemental NDA are related to labeling. Relative to labeling, the Division of Drug Risk Evaluation (DDRE) was consulted for a safety review for Premarin® Vaginal Cream. The WebVDME data mining application from Lincoln Technologies was searched on January 14, 2008 using the trade name Premarin®. In addition, the Adverse Event Reporting System (AERS) was searched. The data mining application and AERS database searches for Premarin® Vaginal Cream did

not identify any unlabeled adverse event terms for consideration as additions to the proposed labeling

Input from the Study Endpoint and Labeling (SEALD) Office of New Drugs was sought on the Physician Labeling. The extensive recommendations from SEALD relative to the Physician Labeling Rule (PLR) were received on June 3, 2008, reviewed and incorporated to a high degree in the attached Physician Insert (PI) provided to Wyeth on July 2, 2008.

Input from Division of Risk Management (DRISK) was sought on Patient Package Insert (PPI). Comments from DRISK, received June 30, 2008, focused on simplification of the wording in the PPI, assuring that the information in the PPI is consistent with PI, removing redundancy in the PPI and assessing the Patient Instruction for Use. Comments from DRISK were incorporated in to the PPI labeling recommendations provided to Wyeth on July 2, 2008.

Input from Division of Medication Error Prevention (DMEP) was sought on the PI, PPI, and container and carton label. The DMEP consult receive on March 21, 2008 did not provide any recommendations relative to the PI or PPI. (b) (4) [redacted] DMEP recommended that the Sponsor be asked to correct this. Per the Project Manager in the Division of Reproductive and Urologic Products (DRUP) responsible for sNDA 20-216/SE2-060, the comments from DMEP were reviewed by the Chief of the Project Management Staff for DRUP, who without further consultation, made the decision that the DMEP comments should not be sent to the Sponsor.

The PI and PPI labeling recommendations, as attached to this review, were sent to the Sponsor on July 2, 2008. This reviewer notes that the efficacy table to be completed by the Sponsor should contain the symptom efficacy information from the subset population of subjects who at baseline met the entrance criteria for symptoms, vaginal pH and superficial cells. Further, because 0.5 g PVC delivered for 7 consecutive days is noted to have systemic exposure, class labeling (including BOXED WARNINGS and WARNINGS AND PRECAUTIONS for Cardiovascular Disorders and Endometrial Cancer) previously applied to estrogen alone products with delivery routes known to produce systemic exposure (i.e. orally delivered products) is also recommended for PVC.

As of the date of this memorandum, the Sponsor is in the process of preparing their response to the Agency's recommendation. Wyeth notes that they will not have a response to the Agency's labeling recommendations until after the Action date of July 25, 2008. (b) (4) [redacted]

(b) (4)

I recommend an Approvable action for this cycle.

Shelley R. Slaughter, M.D., PhD
Medical Officer Team Leader and
Group Leader for NDA 20-216

Attachment
Final PVC Labeling Recommendation – July 2, 2008

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

/s/

Shelley Slaughter
7/25/2008 02:27:34 PM
MEDICAL OFFICER
Approvable action is recommended.

Scott Monroe
7/25/2008 02:39:57 PM
MEDICAL OFFICER
I concur with Dr. Slaughter’s overall assessment and her recommendation that this efficacy supplement is Approvable

CLINICAL REVIEW

Application Type	Supplemental NDA
Submission Number	20-216
Submission Code	SE2-060
Letter Date	September 25, 2007
Stamp Date	September 25, 2007
PDUFA Goal Date	July 25, 2008
Reviewer Name	Theresa H. van der Vlugt, MD
Review Completion Date	June 10, 2008
Established Name	Conjugated estrogens vaginal cream
(Proposed) Trade Name	Premarin® Vaginal Cream
Therapeutic Class	Estrogen
Applicant	Wyeth Pharmaceuticals, Inc.
Priority Designation	Standard
Formulation	Vaginal cream
Dosing Regimen	0.3 mg (0.5 gram) twice weekly, Monday and Thursday 0.3 mg (0.5 gram) daily for 21 days, then 7 days off
Indication	"Treatment of vulvar vaginal atrophy (VVA), dyspareunia associated with VVA or kraurosis vulvae"
Intended Population	Postmenopausal women

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The reviewer recommends approval of 0.3 mg Premarin® Vaginal Cream (0.5 gram containing 0.625 mg of conjugated estrogens per gram of cream) inserted vaginally twice weekly (for example, Monday and Thursday) for the treatment of moderate to severe pain associated with sexual activity (dyspareunia) due to menopause. The reviewer also recommends approval of 0.3 mg Premarin® Vaginal Cream (0.5 gram) inserted vaginally daily for 21 days, then off for 7 days for the treatment of moderate to severe dyspareunia due to menopause. Sufficient evidence is provided in the application to conclude that 0.3 mg Premarin® Vaginal Cream inserted vaginally twice weekly or daily for 21 days, then off for 7 days provides relief in the treatment of moderate to severe dyspareunia due to menopause. The safety of this product is not a major concern. The reported serious and common adverse events are consistent with other intravaginal estrogen hormone products approved to treat moderate to severe symptoms of vulvar and vaginal atrophy due to menopause.

For the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, the Agency's 2003 draft Guidance for Industry entitled "Estrogen and Estrogen/Progestin Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation" recommends that one or more 12-week, randomized, double-blind, placebo-controlled clinical trials be conducted that:

1. have appropriate inclusion and exclusion criteria;
2. conduct appropriate study analyses; and
3. evaluate the following three co-primary endpoints:

- Mean change from baseline to week 12 in the vaginal maturation index (proportions of superficial and parabasal cells). For study inclusion, study participants would have no greater than 5 percent superficial cells on a vaginal smear. The primary efficacy analysis should show a statistically significant increase in superficial cells and a corresponding statistically significant decrease in parabasal cells.

- Mean change from baseline to week 12 in vaginal pH. For study inclusion, study participants would have a vaginal pH > 5.0. The primary efficacy analysis should show a statistically significant lowering of vaginal pH.

- Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome to her. For study inclusion, study participants would have self-identified at least one moderate to severe vulvar and vaginal atrophy symptom. The primary efficacy analysis should show statistically significant improvement in the moderate to severe symptom identified by the subject as most

bothersome. The recommended subject self-assessed symptoms of vulvar and vaginal atrophy include:

1. Vaginal dryness (categorized as none, mild, moderate or severe).
2. Vaginal and/or vulvar irritation/itching (categorized as none, mild, moderate or severe).
3. Vaginal pain associated with sexual activity (categorized as none, mild, moderate or severe).
4. Vaginal bleeding associated with sexual activity (categorized as none, mild, moderate or severe).

The Division of Reproductive and Urologic Products (DRUP) accepts that for number 3 above (vaginal pain associated with sexual activity) and number 4 above (vaginal bleeding associated with sexual activity) that a subject's response might be NA = not applicable because of the absence of sexual activity in the reporting period.

Wyeth Pharmaceuticals Inc., P.O. Box 8299, Philadelphia, PA 19101-8299 is the Applicant for sNDA 20-216/SE2-060.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No postmarketing risk management activities are recommended.

1.2.2 Required Phase 4 Commitments

No Phase 4 clinical study commitment is proposed.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

In 1946, under NDA 05-900, Premarin® (conjugated estrogens, USP) Cream was marketed for vaginal use for atrophic vaginitis and for topical use for acne vulgaris. In 1949, Premarin®

Vaginal Cream was developed and labeled in "the treatment of atrophic vaginitis and kraurosis vulvae".

In a *Federal Register* notice (DESI 2238; Docket No. FDC-D-500 [now Docket No. 76N-0261]) published in July 27, 1972 (37 FR 15028), the FDA announced its conclusion that various drug products, including Premarin® Vaginal Cream, were effective in the treatment of atrophic vaginitis and kraurosis vulvae. On October 3, 1972, Ayerst Laboratories, a Division of the American Home Products Corp., now Wyeth Pharmaceutical Inc., filed ANDA 83-273 for Premarin® Vaginal Cream (0.625 mg of conjugated estrogens, USP per gram of cream). ANDA 83-273 was subsequently approved on October 16, 1978 for the treatment of atrophic vaginitis and kraurosis vulvae. Approved dosages range from 0.5 grams (approximately 0.3 mg of conjugated estrogens) to 2.0 grams (approximately 1.25 mg of conjugated estrogens) applied cyclically (daily for three weeks, then one week off) of a 28-day cycle. In 1991, ANDA 83-273 was renumbered to NDA 20-216 when the Division of Metabolic and Endocrine Products (DMEP) assumed responsibility for Premarin® Vaginal Cream.

The investigational new drug (IND) application for the clinical evaluation of a new dosage regimen for Premarin® Vaginal Cream was submitted to the Division of Reproductive and Urologic Products (DRUP) on June 16, 2005. Two studies have been conducted under IND 72,606: Study 0713S5-413-NA, "Efficacy and Safety of 2 Low Dose Regimens of Conjugated Estrogen Cream Administered Vaginally in Postmenopausal Women with Atrophic Vaginitis", and Study 0713S5-414-US, "A Multiple-Dose, Comparative Bioavailability Study of Premarin Vaginal Cream Versus Premarin Oral Tablets in Postmenopausal Women with Atrophic Vaginitis".

The primary source of efficacy data submitted in support of a vulvar and vaginal atrophy (VVA) indication is single, 52-week Phase 3b Study 0713S5-413-NA. Study 0713S5-413-NA consisted of a 12-week double-blind, placebo-controlled phase and a 40-week open-label phase during which subjects assigned to the placebo groups during the 12-week double-blind phase received Premarin® Vaginal Cream, but were tabulated in the treatment groups to which they were originally assigned.

During the 12-week double-blind phase in Study 0713S5-413-NA, subjects were randomized to receive:

- Premarin® Vaginal Cream 0.3 mg (0.5 gram) daily for 21 days, then 7 days off (PVC 21/7)
- Placebo cream 0.5 gram daily for 21 days, then 7 days off (Placebo 21/7)
- Premarin® Vaginal Cream 0.3 mg (0.5 gram) twice weekly (for example Monday and Thursday) (PVC 2x/wk)
- Placebo cream 0.5 gram twice weekly (for example, Monday and Thursday) (Placebo 2x/wk)

During the 40-week open-label phase of Study 0713S5-413-NA, subjects originally randomized to receive Placebo 21/7 received PVC 21/7. Likewise, subjects originally randomized to receive Placebo 2x/wk received PVC 2x/wk.

The primary source of safety data submitted in Supplemental NDA 20-216/SE2-060 was also Phase 3b, 52-week Study 0713S5-413.NA. A total of 423 treated subjects are represented. Two hundred and eighty-three (283) subjects received Premarin® Vaginal Cream (143 subjects received PVC 21/7 and 140 subjects received PVC 2x/wk) during the double-blind phase of Study 0713S5-413-NA. One hundred forty (140) subjects received Placebo cream during the double-blind phase of Study 0713S5-413-NA. During the 40-week open label phase, a total of 394 subjects received Premarin® Vaginal Cream (198 subjects received PVC 21/7 and 196 subjects received PVC 2x/wk).

1.3.2 Efficacy

The Agency requested data submitted by the Applicant on December 13, 2007 that included in analyses of mean change from baseline to week 12 for those subjects who:

- had no more than 5 percent superficial cells on a vaginal smear
- had a baseline vaginal pH of 5 or greater
- reported a moderate to severe most bothersome vaginal symptom with a severity score of 2 or greater (based on a score of moderate = 2 and severe = 3)

The vaginal maturation index results from this subset analysis from 12-week, double-blind, placebo-controlled, Phase 3b Study 0713S5-413-NA demonstrate the effectiveness of the 0.3 mg (0.5 gram) PVC 2x/wk and the 0.3 mg (0.5 gram) PVC 21/7 treatment groups in producing a statistically significant increase in vaginal superficial cells ($p<0.001$), and a corresponding statistically significant decrease in vaginal parabasal cells ($p<0.001$). The mean change from baseline to week 12 in the vaginal maturation index (proportion of superficial and parabasal cells) is one of the three recommended co-primary endpoints for a VVA indication.

The vaginal pH results from this subset analysis from 12-week, primary, Phase 3b Study 0713S5-413-NA demonstrate the effectiveness of the 0.3 mg (0.5 gram) PVC 2x/wk and the 0.3 mg (0.5 gram) PVC 21/7 treatment groups in producing a statistically significant reduction in vaginal pH between baseline and week 12 compared to placebo ($p<0.001$). The mean change from baseline to week 12 in vaginal pH is a second recommended co-primary endpoint for a VVA indication.

The most bothersome symptom results from this subset analysis from 12-week, primary, Phase 3b Study 0713S5-413-NA demonstrate the effectiveness of the 0.3 mg (0.5 gram) PVC 2x/wk and the 0.3 mg (0.5 gram) PVC 21/7 treatment groups in producing a statistically significant reduction in moderate to severe pain associated with sexual activity (dyspareunia) between baseline and week 12 compared to placebo ($p=0.01$ for PVC 2x/wk and $P<0.001$ for PCV21/7). The mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome to her is a third co-primary endpoint for a VVA indication.

Based on subset analyses presented in the sNDA 20-216/SE2-060 submission, the reviewer recommends that the 0.3 mg (0.5 gram) PVC 21/7 and 0.3 mg (0.5 gram) PVC 2x/week dosing regimens be approved for the treatment of moderate to severe pain with intercourse (dyspareunia), symptom of vulvar and vaginal atrophy, due to menopause..

1.3.3 Safety

The safety data presented in the submission demonstrates that the overall safety profile of 0.3 mg (0.5 gram) Premarin® Vaginal Cream, administered either twice weekly continuously (PVC 2x/wk) or daily for 21 days then off for 7 days (PVC 21/7), is acceptable. Both dosing regimens of Premarin® Vaginal Cream were well tolerated.

No deaths occurred during the conduct of 52-week Study 0713S5-413.NA.

In total, 11 subjects experienced serious adverse events (SAEs) during the double-blind and open-label treatment phases of Study 0713S5-413-NA (5 during the double-blind phase and 6 during the open-label phase). These 11 reported SAEs do not raise safety issues for Premarin® Vaginal Cream.

The most common adverse events across the 4 treatment groups in both the double-blind and open-label phases of Study 0713 S%-413-NA were in the body as a whole system (abdominal pain, headache, and pelvic pain). Vaginitis, under the urogenital system, was also commonly reported during the open-label phase. The common adverse events reported in Study 0713S5-413-NA are not unknown with estrogen alone therapy and have been reported to occur in other clinical trials of hormone therapy conducted for a VVA indication.

Overall, the percentage of subjects discontinuing due to an adverse event during 52-week Study 0713S5-413-NA was small (3.1%; 13 of 423 treated subjects during the 12-week double-blind phase and 3.3%, 13 of 394 treated subjects during the 40-week open-label phase). However, the PVC 21/7 treatment group reported more discontinuations than the PVC 2x/wk treatment group during both phase of Study 0713S5-413-NA. Discontinuations during the double-blind phase were due to headache, pelvic pain, abdominal pain, rash, and vaginitis. Discontinuations during the open-label phase were due to pruritis, deep vein thrombosis, vaginal hemorrhage, vulvovaginal disorder, headache, and pelvic pain. The reported discontinuations due to adverse events during 52-week Study 0713S5-413-NA do not raise safety issues.

Thirty (30) subjects (7.1%, 30 of 423 subjects in the MITT population) had a change from a normal endometrium at baseline as measured by transvaginal ultrasound (TVU) to an abnormal endometrial thickness of ≥ 5 mm at week 52 or at early termination. Only one of these 30 subjects was evaluated for vaginal bleeding (Subject (b) (6) in the PVC 21/7 treatment group; week 26). This subject was reported to have a proliferative endometrium at week 26 and endometrial atrophy at week 52.

From the reported findings in 52-week Study 0713S5-413-NA, twice as many subjects in the PVC 21/7 treatment group experienced endometrial thickness (13 subjects) than in the PVC 2x/wk treatment group (7 subjects) after the full 52 weeks of Premarin® Vaginal Cream use. However, no difference was noted between the two PVC treatment regimens over 40 weeks of use during the open-label phase (5 subjects each per treatment regimen). Two subjects with TVU results > 5 mm were reported to have proliferative endometrium at week 52 (Subject (b) (6) in the PVC 21/7 treatment group and Subject (b) (6) in the PVC 2x/wk treatment group).

Endometrial biopsies were performed at baseline and end-of study. Twelve (12) subjects with endometrial biopsy results at end-of-study were reported to have proliferative endometrium (6 cases of proliferative endometrium in the PVC 21/7 treatment groups and 6 cases in the PVC 2x/wk treatment groups). The occurrence of proliferative endometrium is not unexpected when a woman with a uterus is treated with unopposed estrogen. It is important, however, that labeling advise patients and healthcare providers of the need for close clinical surveillance, including adequate diagnostic measure in all cases of postmenopausal vaginal bleeding. The addition of a progestin is generally recommended for women with a uterus to reduce the chance of getting cancer of the uterus.

1.3.4 Dosing Regimen and Administration

Each gram of Premarin® Vaginal Cream contains 0.625 mg of conjugated estrogens, USP. Premarin® Vaginal Cream is only intended for intravaginal use in postmenopausal women.

Premarin® (conjugated estrogens, USP) is approved for use as a tablet (0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg and 1.25 mg). Premarin® Vaginal Cream (conjugated estrogens, USP; 0.5 gram to 2.0 gram), administered in a cyclic regimen of three weeks on and 1 week off, is currently approved for the treatment of atrophic vaginitis and kraurosis vulvae.

1.3.5 Drug-Drug Interactions

No drug-drug interactions were studied in the Premarin® Vaginal Cream clinical development program.

In vitro and in vivo studies of other estrogen drug products have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations, phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effect and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects. This information will be provided in labeling

1.3.6 Special Populations

Premarin® Vaginal Cream is only intended for use in postmenopausal women. There were insufficient numbers of geriatric subjects in primary, Phase 3b Study 0713S5-413-NA to determine if those over 65 years of age differ from younger subjects in their response to Premarin® Vaginal Cream.

Premarin® Vaginal Cream was not studied in women with liver disease or renal impairment. Premarin® Vaginal Cream should not be used in pregnant women.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

In 1946, under NDA 05-900, Premarin® (conjugated estrogens, USP) Cream was marketed for vaginal use for atrophic vaginitis and for topical use for acne vulgaris. In 1949, Premarin® Vaginal Cream was developed and labeled in "the treatment of atrophic vaginitis and kraurosis vulvae". The originally developed Premarin® Cream was relabeled for the acne vulgaris indication only. Premarin® Cream was withdrawn from the market in 1976 when "found to be less than effective for acne vulgaris".

In a *Federal Register* notice (DESI 2238; Docket No. FDC-D-500 [now Docket No. 76N-0261]) published in July 27, 1972 (37 FR 15028), the FDA announced its conclusion that various drug products, including Premarin® Vaginal Cream were effective in the treatment of atrophic vaginitis and kraurosis vulvae. On October 3, 1972, Ayerst Laboratories, a Division of the American Home Products Corp., now Wyeth Pharmaceutical Inc., filed ANDA 83-273 for Premarin® Vaginal Cream (0.625 mg of conjugated estrogens, USP per gram of cream). ANDA 83-273 was subsequently approved on October 16, 1978 for the treatment of atrophic vaginitis and kraurosis vulvae. Approved dosages range from 0.5 grams (approximately 0.3 mg of conjugated estrogens) to 2.0 grams (approximately 1.25 mg of conjugated estrogens) applied cyclically (daily for three weeks, then one week off) of a 28-day cycle. In 1991, ANDA 83-273 was renumbered to NDA 20-216 when the Division of Metabolic and Endocrine Products (DMEP) assumed responsibility for Premarin® Vaginal Cream.

Premarin® Vaginal Cream (PVC) is a naturally derived product composed of a mixture of conjugated estrogens obtained from natural sources, occurring as the sodium salts of water soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains concomitant components, as sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin.

2.2 Currently Available Treatment for Indications

Numerous estrogen alone and estrogen plus progestin drug products are currently approved for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) due to menopause and/or the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause. These include:

- Oral tablet: Activella® (estradiol plus norethindrone acetate), Angeliq® (drospirenone plus estradiol), Cenestin® (synthetic conjugated estrogens, A), Enjuvia™ (synthetic conjugated estrogens, B), Estrace® (estradiol), femhrt® (norethindrone acetate/ethinyl estradiol), Femtrace® (estradiol acetate), Menest® (esterified estrogens), Ortho-Est®

(estropipate), Prefest® (estradiol/norgestimate), Premarin® (conjugated estrogens), Prempro™/Premphase® (conjugated estrogens plus medroxyprogesterone acetate)

- Transdermal system: Alora® (estradiol), Climara® (estradiol), Climara-Pro® (estradiol plus levonorgestrel), Combipatch™ (estradiol plus norethindrone acetate), Esclim® (estradiol), Estraderm® (estradiol), Vivelle® (estradiol), Vivelle-Dot® (estradiol)

- Topical: Divigel® (estradiol gel), Elestrin™ (estradiol gel), Estrasorb® (estradiol topical emulsion), EstroGel® (estradiol gel), Evamist™ (estradiol mist)

- Vaginal: Premarin® Vaginal Cream (conjugated estrogens cream), Estrace® Cream (estradiol cream), Vagifem® (estradiol hemihydrate tablet), Estring® IVR (estradiol ring), Femring® (estradiol ring).

2.3 Availability of Proposed Active Ingredient in the United States

Conjugated estrogens in oral tablet form have been used for VMS and VVA estrogen therapy since 1942 and 1946, respectively. The following oral conjugated estrogens products are approved and currently marketed in the U.S.:

Conjugated estrogens alone oral products:	Dosage strengths:
Premarin®	0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg

Conjugated estrogens plus medroxyprogesterone acetate oral product	Dosage strengths:
Prempro™	0.3 mg/1.5 mg, 0.45 mg/1.5 mg, 0.625 mg/2.5 mg, 0.625 mg/5.0 mg
Premphase®	0.625 mg conjugated estrogens (CE) days 1-14, then 0.625 mg CE plus medroxyprogesterone acetate 5.0 mg days 15-28

The following vaginal conjugated estrogens product is approved and currently marketed in the U.S.:

Conjugated estrogen vaginal product:	Dosage Strengths:
Premarin® Vaginal Cream	0.5 gram to 2.0 gram per day (0.625 mg CE per gram)

2.4 Important Issues With Pharmacologically Related Products

After an average follow-up of 5.2 years, the conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) substudy of the Women's Health Initiative (WHI) study was stopped early (year 2002) because the increased risk of breast cancer and cardiovascular events exceeded the specified benefits in the "Global Index". Centrally adjudicated data, after an average follow-up of 5.6 years, reported an increased risk of invasive breast cancer (relative risk [RR] of 1.24 with a 95% nominal confidence interval [nCI], 1.01-1.54), increased risk of all strokes (RR 1.31, 95% CI, 1.02-1.68) and ischemic stroke (RR 1.44, 95% CI, 1.09-1.90), increased risk of coronary heart disease (RR 1.23, 95% CI, 0.99-1.53), increased risk of probable dementia (RR 2.05, 95 percent CI, 1.21-3.48), and a decreased risk of hip fracture (RR 0.67, 95 percent CI, 0.47-0.96).

The risk and benefit information available in the WHI substudy in year 2002 prompted changes in labeling for estrogen class drug products including, but not limited to, the addition of a boxed warning to all estrogen plus progestin product labels and the expansion of the existing boxed warning in all estrogen alone product labels to include the increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis reported in the WHI estrogen plus progestin substudy. In addition, boxed warning information states that "---in the absence of comparable data, these risks should be assumed to be similar" for "other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestin", and that "---estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual women."

After an average follow-up of 6.8 years, the WHI conjugated estrogens alone substudy was also stopped early (year 2004) because the use of CE alone increased the risk of stroke (RR 1.39, 95% nCI, 1.10-1.77) (conjugated estrogens alone versus placebo), and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen alone in predetermined primary endpoints. Other findings in the conjugated estrogens alone clinical trial included a decreased risk of hip fracture (RR 0.61, 95% nCI, 0.41-0.91), no effect on coronary heart disease (RR 0.91, 95% nCI 0.75-1.12), a decreased risk of invasive breast cancer (RR 0.77, 95% nCI, 0.59-1.01), an increased risk of probable dementia (RR 1.49, 95% nCI, 0.83-2.66), and no decrease in mild cognitive impairment (RR 1.34, 95% CI, 0.95-1.89).

Centrally adjudicated results reported for the WHI estrogen alone substudy, after an average follow-up of 7.1 years, reported an increased risk for all strokes (RR 1.37, 95% nCI, 1.09-1.73) (CE versus placebo) and ischemic stroke (RR 1.55, 95% nCI, 1.19-2.01). No effect on coronary heart disease, after an average follow-up of 7.1 years, was reported (RR 0.95, 95% nCI, 0.78-1.16). Other findings in the CE alone substudy, based on an average follow-up of 7.1 years, included a decreased risk of hip fracture (RR 0.65, 95% nCI, 0.45-0.94), a decreased risk of invasive breast cancer (RR 0.80, 95% nCI, 0.62-1.04), and an increased risk for probable dementia (RR 1.49, 95% CI, 0.83-2.66).

The risk and benefit information available in the estrogen alone WHI substudy in year 2004 prompted changes in labeling for estrogen class drug products including, but not limited to, the expansion of the boxed warning to include the reported increased risk of stroke in the estrogen alone WHI substudy. In years 2006 and 2007, additional changes were made in labeling for estrogen class drug products based on centrally adjudicated results for the WHI estrogen alone substudy.

Risk information available in the Women's Health Initiative Memory Study (WHIMS) in years 2003 and 2004 prompted additional changes in labeling for estrogen class drug products to include the reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older. WHIMS findings for both the estrogen alone substudy and the estrogen plus progestin substudy were added to the boxed warning, and the clinical studies, warnings and precautions sections of estrogen class labeling.

2.5 Presubmission Regulatory Activity

The investigational new drug (IND) application for the clinical evaluation of a new dosage regimen for Premarin® Vaginal Cream was submitted to the Division of Reproductive and Urologic Products (DRUP) on June 16, 2005. The initial study conducted under IND 72,606 was Study 0713S5-413-NA titled, "Efficacy and Safety of 2 Low Dose regimens of Conjugated Estrogen Cream Administered Vaginally in Postmenopausal Women with Atrophic Vaginitis".

On September 1, 2005, DRUP provided Wyeth Pharmaceuticals with several comments and recommendations regarding Study 0713S5-413-NA:

"Clinical:

1. For the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, the Agency recommends three co-primary endpoints:

   ● Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome to her. For study inclusion, study participants would have self-identified at least one moderate to severe vulvar and vaginal atrophy symptom. The primary efficacy analysis should show statistically significant improvement in the moderate to severe symptom identified by the subject as most bothersome.
   ● Mean change from baseline to week 12 in vaginal pH. For study inclusion, study participants would have a vaginal pH > 5.0. The primary efficacy analysis should show a statistically significant lowering of vaginal pH.
   ● Mean change from baseline to week 12 in the vaginal maturation index (proportions of superficial and parabasal cells). For study inclusion, study participants would have no greater than 5 percent superficial cells on a vaginal smear. The primary efficacy analysis should show a statistically significant increase in superficial cells and a statistically significant decrease in parabasal cells.

2. Per the Agency's 2003 draft clinical evaluation Guidance for Industry, we recommend that you modify the one stated primary endpoint to demonstrate not only a statistically significant increase in superficial cells but a corresponding statistically significant decrease in parabasal cells.

3. We recommend that the primary objective of Study 0713S5-413-NA be modified to include the two additional co-primary endpoints recommended in the Agency's 2003 draft Guidance for Industry, namely, change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome to her, and change from baseline to week 12 in vaginal pH. In the protocol submitted, vaginal pH will be obtained by the investigator as part of the Genital Health Clinical Evaluation (GHCE) at screening, weeks 4, 6, 12, and 52 as a secondary objective.

4. Be advised that the absence of identification of the baseline moderate to severe symptom identified by the patient as being the most bothersome to her would be a review issue.

5. For study inclusion, we recommend a vaginal pH of > 5.0 as an inclusion criterion.

6. Prior to initiation of Study 0713S5-413-NA, we recommend that you consider conducting a postmenopausal women focus group to determine which vaginal symptoms are most commonly identified as bothersome for which the postmenopausal woman would seek treatment. Based on the results of the focus group, the proposed vaginal symptoms to be self-assessed in Study 0713S5-413-NA could be revised accordingly.

7. Be advised that no results of the GHCE investigator measurement would be considered in determining the effectiveness of the drug product, and no findings from the GHCE would appear in labeling.

8. Your proposed exclusion criteria appear appropriate.

9. The proposed procedures to be performed at baseline and weeks 4 and 6 appear appropriate. The proposed procedures to be performed at week 12 appear appropriate with one exception. At week 12, no routine transvaginal ultrasound (TVU) and endometrial biopsy is proposed. Per the Agency's 2003 draft Guidance for Industry, we recommend that all subjects who have a uterus should undergo an endometrial biopsy at baseline and week 12 as safety assessments. If the week 12 endometrial biopsy confirms insufficient endometrial tissue for diagnosis, after a valid attempt is made to sample the endometrium, a transvaginal double-wall endometrial thickness of ≤ 4 mm could be considered not indicative of endometrial hyperplasia.

10. The proposed procedures to be performed at week 52 in Study 0713S5-413-NA appear appropriate except for the conduct of an endometrial biopsy for subjects with an endometrial thickness of ≥ 5 mm. We recommend that all subjects who have a uterus undergo an endometrial biopsy at week 52 as a safety assessment (not just those with a TVUS ≥ 5mm).

If the week 52 endometrial biopsy confirms insufficient endometrial tissue for diagnosis, after a valid attempt is made to sample the endometrium, a transvaginal double-wall endometrial thickness of ≤ 4 mm could be considered not indicative of endometrial hyperplasia.

11. We recommend that the mean change in the most bothersome symptom between baseline and week 12 should be calculated as one of the three recommended co-primary analyses. In addition, as secondary analyses, you may submit subset analyses to demonstrate the mean change from baseline to week 12 for each of the gynecologic symptoms included in the symptom assessment questionnaire. A composite score analysis of all four vaginal symptoms to demonstrate the mean change from baseline to week 12 could also be submitted as a secondary analysis.

12. We recommend that the mean change in vaginal pH between baseline and week 12 be calculated as one of the three recommended co-primary analyses."

"Chemistry:

1. The proposed acceptance criteria for conjugated estrogens in the placebo formulation should be explained and justified. The origin of any amount of API in the placebo must be specified.

2. Certificates of Analysis for any placebo batches used in the proposed clinical study must be provided.

3. A side by side comparison of the quantitative formulations for the placebo and active drug product must be provided."

"Statistics:

1. It is not appropriate to combine the placebo groups for the analyses. The treatment regimen is not blinded. Section 19.2 should be revised for each treatment regimen to be compared to only the matching placebo group.

2. The Sponsor will need to recalculate the sample size to ensure sufficient power for the desired comparisons without combining placebo groups (Section 10.1).

3. The other parts of the statistics section are appropriate."

Wyeth Pharmaceuticals responded on October 14, 2005:

Clinical:

1. Wyeth agreed to change the primary endpoint for vaginal maturation index to demonstrate a statistically significant increase in superficial cells and a statistically significant decrease in parabasal cells.

2. Wyeth agreed to include 2 additional co-primary endpoints, change in baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome to her and change in baseline to week 12 in vaginal pH.

3. Wyeth proposed to change the inclusion criterion to a reading of vaginal pH $\geq$ 5.0 (rather than > 5.0). "The color indicator on the pH tape dispensers used is for pH readings of 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, or 7.5. If we change the pH for inclusion to > 5.0, patients with a vaginal pH reading of 5.1 or 5.2 will probably be recorded as 5.0 and they will not be eligible to enter the study."

4. Wyeth will require an endometrial biopsy for all subjects at week 52. We will also require a biopsy at early termination for any patient who terminates after 12 weeks, or who experiences abnormal vaginal bleeding at anytime during the study. For the post-baseline time points, the TVU endpoint can be used if it is not possible to obtain sufficient endometrial tissue for diagnosis.

5. Wyeth agreed with the Agency's recommendations for the co-primary endpoint analyses and subset analyses.

Chemistry:

1. "There is no API added in any amount in the placebo cream. This is confirmed by the performance of the HPLC analytical method 3135-103. The specification applicable to this test is "Absent".

2. A Certificate of Analysis for the placebo was provided.

3. A side by side comparison of the quantitative formulations for the placebo and active drug product was provided."

Statistics:

1. Wyeth revised the statistical methods section so that each treatment group will be compared to the matching placebo group.

2. The sample size was reviewed based on the additional co-primary endpoints as well as the requirement that the placebo groups cannot be combined.

Medical Officer's Comment's:

The Applicant obtained endometrial biopsies at end-of-study (week 52), at early termination (if termination date was on or after week 12), and to evaluate abnormal bleeding that occurred at any point during the conduct of Study 0713S5-413-NA. This reviewer concurred with the October 14, 2005 protocol changes. Study 0713S5-413-NA was a planned 52-week study to assess endometrial safety

On November 21, 2005, Wyeth Pharmaceuticals submitted Study 0713S5-414-US titled, "A Multiple-Dose, Comparative Bioavailability Study of Premarin Vaginal Cream Versus Premarin Oral Tablets in Postmenopausal Women with Atrophic Vaginitis".

On February 23, 2006, Amendment Number 1 for Study 0713S5-413-NA was submitted. The revisions were as follows:

1. The primary endpoint for vaginal maturation index (VMI) was modified to include the percentage of parabasal cells to demonstrate a statistically significant decrease in parabasal cells.
2. The change in vaginal pH from baseline to week 12 was added as a co-primary endpoint.
3. The change in symptom score from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome has been added as a co-primary endpoint.

Amendment Number 2 for Study 0713S5-413-NA was submitted on February 8, 2007. This amendment provided for the collection of additional blood samples at weeks 6, 7, 26 and 52 at selected sites to measure serum estrone and estradiol levels.

On March 19, 2007, Wyeth Pharmaceuticals submitted the statistical analysis plan (SAP) for Study 0713S5-413-NA. The SAP was revised on April 4, 2007, and per the submission, Study 0713S5-413-NA was unblinded on April 9, 2007. The revisions were as follows:

1. Criteria for subjects to be included in the efficacy evaluable population have been added as subsections, "Criteria applying to all efficacy endpoints", and "Criteria specific to each endpoint".
2. The following paragraph was added to change from baseline of the most bothersome symptom: "To assess the sensitivity of this endpoint, an alternate definition of the baseline score will be defined. This alternate definition will be the severity score recorded for the most bothersome symptom at the screening visit. The change from baseline will be calculated using this baseline value and analyzed similarly to the primary definition."
3. The following statement was removed from the diary card individual symptoms scores: "The analyses for individual symptoms will be restricted to only those women who have at least average severity of at least moderate (2) of that given symptom during the baseline week".
4. The criterion for pulse was revised from ≤ 60 beats per minute or ≥ 100 beats per minute to ≤ 50 beats per minute or ≥ 100 beats per minute.

On October 3, 2007 and October 10, 2007, new investigator information pertaining to Study 0713S5-413-NA was provided.

2.6 Other Relevant Background Information

Premarin® Vaginal Cream has been marketed in the United States for over 50 years and approved for approximately 30 years

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Per the approved labeling, each gram Premarin® Vaginal Cream contains 0.625 mg conjugated estrogens, USP in a nonliquefying base containing cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, benzyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil. Premarin® Vaginal Cream is applied intravaginally.

Premarin® Vaginal Cream (PVC) is a naturally derived product composed of a mixture of conjugated estrogen obtained from natural sources, occurring as the sodium salts of water soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains concomitant components, as sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin.

The currently approved drug product, Premarin® Vaginal Cream, was used in Phase 3b Study 0713S5-413-NA and Phase 1 Study 0713S5-414-US. The product was packaged into the same 8-gram tubes as are used for the commercial product and labeled with clinical labels.

FDA is authorized to refer to Wyeth's original NDA 20-216 submission for active drug substance and drug product for CMC information.

Medical Officer's Comments:

On September 25, 2007, Wyeth Pharmaceuticals submitted the approved Premarin® Vaginal Cream carton labeling, container label, and the prescribing information and package insert to the Division of Medication Error Prevention (DMEP) for review. The Division of Reproductive and Urologic Products (DRUP) received a review from DMEP for Premarin® Vaginal Cream on March 21, 2008. DMEP provided the following information:

1. *A search of the Agency's Adverse Events Reporting System (AERS) did not "retrieve any cases of postmarketing confusion with the nomenclature for the product line or the Premarin® Vaginal Cream labels or labeling."*
2. *A review of the container label and carton labeling identified several potential sources of medication errors:*

- (b) (4)
- (b) (4)

Per the DMEP review, (b) (4)

Relocating this statement to a less prominent location will allow the health care professional to focus on the important information such as the propriety and established names, and dosage form." (b) (4) *Both of these statements are more prominent than the proprietary and established names. Thus, these yellow highlighted statements distract from important information such as the proprietary and established name."*

DMEP did not provide comments on the prescribing information and package insert.

DMEP requested that the following comments be communicated to Wyeth Pharmaceuticals:

1. (b) (4)
2. (b) (4)

Wyeth Pharmaceuticals was not advised of DMEP recommendations during this review cycle.

Per the Chemistry, Manufacturing and Controls Review dated March 19, 2008, "no changes are proposed in the approved chemistry, manufacturing and controls. Additionally, no changes have been made to the chemistry section of labeling.

An Environmental Assessment (EA) section has been provided and is evaluated as follows:

"Environmental Assessment (9-Nov-2007 submission)
The sponsor provides statements that the proposed supplement for a lower dosage regimen will not increase the use of the active moiety. Therefore, an Environmental Assessment to address an increased amount of active is not required, according to 21 CFR 25.3(a). The CMC reviewer indicates that the request for exclusion from the requirement for an Environmental Assessment is justified."

3.2 Animal Pharmacology/Toxicology

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

Medical Officer's Comments:

Please refer to the original NDA 20-216 submission for animal pharmacology and toxicology information.

Per the Pharmacology/Toxicology Review and Evaluation dated March 6, 2008:

- *"Nonclinical data support approval."*
- *"No new clinical studies are required."*
- *"Sponsor has proposed acceptable revised labeling in PLR format."*

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Study 0713S5-413-NA titled, "Efficacy and Safety of 2 Low-Dose Regimens of Conjugated Estrogen Cream Administered Vaginally in Postmenopausal Women with Atrophic Vaginitis" was the primary, Phase 3b, 52-week (first 12 weeks were double-blind; followed by 40-weeks open-label), prospective, randomized, placebo-controlled study conducted to support the safety and effectiveness of 0.3 mg (0.5 gram conjugated estrogens) Premarin® Vaginal Cream administered intravaginally for the treatment of postmenopausal women with moderate to severe symptoms of vulvar and vaginal atrophy due to menopause.

The primary objective of Study 0713S5-413-NA was to evaluate the efficacy of 2 low-dose Premarin® Vaginal Cream (PVC) regimens in the treatment of atrophic vaginitis after 12 weeks of treatment: the labeled regimen (0.3 mg [0.5 gram]) once daily for 21 days, then off for 7 days, and an intermittent regimen of 0.3 mg (0.5 gram) twice weekly. The secondary objectives were to evaluate the effect of PVC treatment of atrophic vaginitis at intermediate time points, and endometrial safety at week 52.

Subjects were randomized in a 2:1 ratio (active treatment: placebo) to 1 of 4 treatment groups as follows:

- 0.3 mg (0.5 gram) Premarin® Vaginal Cream inserted vaginally twice weekly (for example, Monday and Thursday) (PVC 2x/week)
- 0.5 gram Placebo cream inserted vaginally twice weekly (placebo 2x/wk)

- 0.3 mg (0.5 gram) Premarin® Vaginal Cream inserted vaginally daily for 21 days followed by 7 days off (PVC 21/7)
- 0.5 gram Placebo cream inserted vaginally daily for 21 days followed by 7 days off (placebo 2x/wk)

During the open-label portion of Study 0713S5-413-NA subjects assigned to the placebo groups during the 12-week double-blind portion of Study 0713S5-413-NA received PVC, but were tabulated in the treatment groups to which they were originally randomly assigned (placebo 21/7 to PVC 21/7 and placebo 2x/wk to PVC 2x/wk).

At the time of the submission of sNDA 20-216/SE2-060, the 40-week open-label extension of Study 0713S5-413-NA was ongoing.

On January 25, 2008, Wyeth Pharmaceuticals submitted the 4-Month Safety Update for sNDA 20-216/SE2-060. The 4-Month Safety Update included safety information on the full 52 weeks of treatment in Study 0713S5-413-NA.

4.2 Tables of Clinical Studies

Table 1 includes the Phase 3b clinical trial conducted in the Premarin® Vaginal Cream low-dose development program. As previously stated, the open-label 40-week extension of Study 0713S5-413-NA was on-going as of the submission date of September 25, 2007.

Table 1: Premarin Vaginal Cream Clinical Trials

Type of Study Protocol Number	Objectives of the Study	Study Design Type of Control	Test Products; Dosage and Administration; Route of Administration	Number of Subjects	Duration of Treatment	Study Status Type of report
Safety and efficacy 0713S5-413-NA	Efficacy and safety of Premarin® Vaginal Cream in the treatment of vulvar and vaginal atrophy	Outpatient, multicenter, double-blind, randomized, placebo-controlled	0.5 g PVC (0.3 mg CE) twice weekly intravaginally 0.5 g placebo cream twice weekly intravaginally 0.5 g PVC (0.3 mg CE) daily intravaginally for 21 days, then 7 days off 0.5 g placebo	143 72 140	Double-blind: efficacy 12 weeks Open-label: safety 40 weeks	Completed Interim report On-going at the time of the September 25, 2007 submission

			cream daily intravaginally for 21 days, then 7 days off	68		
Comparative bioavailability 0713S5-414-US	Assess the comparative bioavailability of Premarin® Vaginal Cream versus a Premarin® reference tablet	Open-label, randomized, multiple-dose, 2-treatment, 2-period crossover inpatient/outpatient	0.5 g PVC (0.3 mg CE) daily for 7 days 0.3 mg Premarin® tablet	12 12	7 days 7 days	Completed

NA = North America; PVC = Premarin® Vaginal Cream; CE = conjugated estrogens.

4.3 Review Strategy

The primary source of efficacy data submitted in support of a treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) due to menopause indication is the interim report of the 12-week double-blind portion of Phase 3b Study 0713S5-413-NA.

The primary source of safety data is also Phase 3b Study 0713S5-413-NA. The safety data received on September 25, 2007 (sNDA 20-216/SE2-060) included safety results and conclusions related to treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, subject withdrawals, clinical laboratory parameters, vital sign measurements, transvaginal ultrasound (TVU) results, and endometrial biopsy results for the 12-week double-blind portion of Study 0713S5-413-NA. The September 25, 2007 submission also included preliminary results of adverse events (AEs) and SAEs from the open-label portion of Study 0713S5-413-NA included in the database as of April 22, 2007. Limited safety data is also provided in 14-day Phase 1 Study 0713S5-414-US

On January 25, 2008, Wyeth Pharmaceuticals Inc. submitted the 4-Month Safety Update, which provided safety data for the full 52-weeks of Study 0713S5-413-NA.

4.4 Data Quality and Integrity

Per the submission, "Original subject records were reviewed during the course of the periodic monitoring of each clinical study contained in this submission. The purpose of this review was to verify the accuracy of the case report forms submitted to Wyeth Research. Periodic monitoring, as described, was performed in accordance with the Wyeth Research Standard Operating Procedures (SOPs) in effect during the time the studies were active."

On November 6, 2007, Wyeth Pharmaceuticals Inc. was requested to provide the following information (or indicated where such information could be located in the eCTD submission) to assist in determining the need for a Division of Scientific Investigation (DSI) audit:

- Number of subjects randomized per center.
- Number of subjects treated per center.
- Number of subjects discontinued per center.
- Number of protocol violations per center.
- Number of major protocol violations per center.

Wyeth Pharmaceutical Inc. responded on November 21, 2007. From the information received, the following two centers were recommended by the reviewer for Division of Scientific Investigation (DSI) audits:

1. Center 017, Dr. Barry Lubin
   Hampton Rhodes Center for Clinical Research, Inc.
   885 Kempsville Road
   Suite 221
   Norfolk, VA 23502

2. Center 037, Dr. Celine Bouchard
   Clinique RSF Inc.
   Center Medical Berger
   1000, chemin Sainte-Foy
   Bureau 102
   Quebec
   Canada
   G1S 2L6

The Good Clinical Practice Branch I of the Division of Scientific Investigations (DSI) conducted an investigation of Center 037 (Dr. Celine Bouchard) March 3-6, 2008. The DSI Clinical Inspection Summary, submitted to DRUP on April 28, 2008 indicates that there "were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events was noted. Data in sponsor-provided data listings were supported by data in source documents and case report forms. No Form FDA 483, Inspectional Observations, was issued at the close of the inspection." DSI concluded that "data generated for protocol 0713S5-413-NA at this clinical site appear acceptable for use in support of NDA 20-216/060."

The Good Clinical Practice Branch I of the Division of Scientific Investigations (DSI) conducted an investigation of Center 017 (Dr. Barry Lubin) February 25, 2008 - March 1, 2008. The DSI Clinical Inspection Summary, submitted to DRUP on May 9, 2008 indicates that there "were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events was noted. Data in sponsor-provided data listings were supported by data in source documents and case report forms." One instance of protocol deviation was reported. "Subject (b) (6) did not meet the protocol entry criterion requiring a vaginal maturation index (VMI) score of ≤ 5% superficial cells as determined from a vaginal

cytological smear." DSI concluded that "data generated for protocol 0713S5-413-NA at this clinical site appear acceptable for use in support of NDA 20-216/060."

In general, DSI stated that "for the two clinical investigator sites inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoints captured as specified in the protocol."

4.5 Compliance with Good Clinical Practices

The primary, Phase 3b, safety and efficacy Study 0713S5-413-NA appears to have been conducted in accordance with regulations pertaining to Good Clinical Practice (GCP), the International Conference on Harmonization: Good Clinical Practice Consolidation Guidelines, the Code of Federal Regulations (Notice of Availability, *Federal Register* 25692, May 6, 1997), and the Declaration of Helsinki (revised Hong Kong, 1989).

Written informed consent was obtained from all subjects before their enrollment. Each subject was assigned a subject number, which was used on the case report form (CRF) instead of the subject's name. The data were captured using remote data capture (RDC).

4.6 Financial Disclosures

Form FDA 3454 (4/06), dated September 13, 2007, and signed by Gary L. Stiles, MD, Executive Vice President and Chief Medical Officer and Gary Gallagher, Vice President – R & D Finance, Wyeth Pharmaceuticals Inc. was included in the submission. Nine of the of the 49 listed principal investigators for Study 0713S5-413-NA were the recipient of significant payment of other sorts as defined in 21 CFR 54.2(f) – "any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria."

U.S. Investigator:

(b) (6)

Canadian Investigator:

(b) (6)

(b) (6)

Medical Officer's Comments:

No data integrity issues are identified in the financial disclosure information provided with the submission.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

A bioavailability study, Study 0713S5-414-US titled, "A Multiple-Dose, Comparative Bioavailability Study of Premarin Vaginal Cream Versus Premarin Oral Tablets in Postmenopausal Women with Atrophic Vaginitis" was conducted to characterize the systemic exposure and bioavailability at steady state of 0.5 g (0.3 mg) of Premarin® Vaginal Cream (PVC) and 0.3 mg Premarin® oral tablet in postmenopausal women with atrophic vaginitis. This was an open-label, randomized, multiple-dose, 2-treatment, 2-period crossover study conducted in generally healthy postmenopausal women, aged 45 to 80 years (mean age 57.5 years), with atrophic vaginitis. Twenty-four (24) subjects were enrolled and completed the study, and PK data were obtained for all subjects for both PVC and Premarin® tablet formulations.

Premarin® Vaginal Cream (0.5 g [0.3 mg]) and 0.3 mg Premarin® oral tablets were each administered for 7 days: days 1 to 7 (period 1) and days 8 to 14 (period 2). Subjects were randomly assigned to receive either PVC or tablet during the first period. There was no washout period between treatment periods. Both study medications were administered in the morning at approximately the same time each day. The inclusion/exclusion criteria were the same as in primary, Phase 3b Study 0713S5-413-NA.

Blood samples for baseline hormones were collected on day -2, day -1, and day 1 before the first administration of study medication. Serial blood samples for PK analysis were collected on days 7 and 8 of each treatment period at the following times: immediately before dosing for baseline determination) and at 1.5, 3, 4.5, 6, 7.5, 9, 10.5, 12, 16, and 24 hours after dose administration. The PK analysis of plasma concentrations was performed by the Clinical Pharmacokinetics group of Wyeth Research for the following components of Premarin: unconjugated and total (unconjugated plus conjugated) estrone, equilin, and 17β-estradiol. Plasma concentrations for estrone and estradiol were analyzed with and without adjustment for baseline concentrations since both hormones are endogenous in women.

Values for C_{max}, the time to reach C_{max} (t_{max}), and minimum concentration (C_{min}) were calculated. The steady state area under the concentration-time curve (AUC_{ss}) was calculated from zero to τ was the dose interval of 24 hours. Average concentration (C_{avg}) was calculated by AUC_{ss}/τ. Relative bioavailability (F) was calculated as:

$$F = \frac{AUC_{ss} \text{ following vaginal administration}}{AUC_{ss} \text{ following oral administration.}}$$

Per the final study report (CSR-63983), the mean unconjugated estradiol steady state C_{max} (uncorrected for baseline) after daily vaginal administration (7 days) of 0.5 g (0.3 mg) of Premarin® Vaginal Cream was 12.8 ± 16.6 pg/mL versus 19.4 ± 24.7 pg/mL for 0.3 mg Premarin® Tablets. The mean unconjugated estrone steady state C_{max} (uncorrected for baseline) after daily vaginal administration (7 days) of 0.5 g (0.3 mg) of Premarin® Vaginal Cream was 42.0 ± 13.9 pg/mL versus 70.2 ± 32.6 pg/mL for 0.3 mg Premarin® Tablets. Study 0713S5-414-US demonstrates that systemic exposure to estradiol and estrone was lower with Premarin® Vaginal Cream than with Premarin® Tablets (mean relative bioavailability was 81% for unconjugated estradiol and 71% for unconjugated estrone).

Medical Officer's Comments:

(b) (4)

In this submission, the Clinical Pharmacology Reviewer recommends that the pharmacokinetic finding of Study 0713S5-414-US be included in labeling. See the Clinical Pharmacology and Biopharmaceutics Review of sNDA 20-216/SE2-060 for a full discussion of PK issues

5.2 Pharmacodynamics

No pharmacodynamic studies related to efficacy were conducted for Premarin® Vaginal Cream.

5.3 Exposure-Response Relationships

An increased incidence of shifts from baseline TVU measurements < 5 mm to > 5 mm was observed in Study 0713S5-413-NA for both Premarin Vaginal Cream dosing regimens. These findings are discussed further in Section 7.1.3 "Dropouts and Other Significant Adverse Events" of this review.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Premarin® Vaginal Cream (PVC) 0.3 mg to 1.25 mg (0.5 gram to 2.0 gram of PVC containing 0.625 mg of conjugated estrogens per gram) is currently approved in the treatment of atrophic vaginitis and kraurosis vulvae.

sNDA 20-216/SE2-060 is seeking approval of 0.3 mg of PVC for the treatment of "dyspareunia associated with VVA" for 2 dosing regimen: 0.3 mg (0.5 gram) twice weekly (for example, Monday and Thursday) and 0.3 mg (0.5 gram) daily for 3 weeks, then 1 week off.

6.1.1 Methods

The clinical program to evaluate the efficacy and safety of 0.3 mg Premarin® Vaginal Cream included a single, randomized, double-blind, placebo-controlled, Phase 3b Study 0713S5-413-NA. Primary, Phase 3b Study 0713S5-413-NA will be discussed further in this review.

6.1.2 General Discussion of Endpoints

The Agency's 2003 draft clinical evaluation Guidance for Industry recommends three co-primary endpoints for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy to address the resulting estrogen deprived changes in the genitourinary tract. In the vulvar area and vagina, the vaginal epithelium becomes dry and atrophic, which causes inflammation, discomfort, itching, and dyspareunia. A lateral wall vaginal cytology smear (allowing the cytological examination of vaginal mucosa epithelial cells) demonstrates an increased proportion of parabasal vaginal epithelial cells and a decreased proportion of superficial vaginal epithelial cells. Vaginal pH increases from the normal 3.5 to 4.0 (a pH which favors lactobacilli) to 6.0 to 8.0 (a pH which favors pathogenic organisms).

Per the Agency's 2003 draft clinical evaluation guidance document, the Agency recommends that one or more 12-week, randomized, double-blind, placebo-controlled clinical trials be conducted that:

1) have appropriate inclusion and exclusion criteria;
2) conduct appropriate study analyses; and
3) evaluate the following three co-primary endpoints:

- The mean change from baseline to week 12 in the vaginal maturation index (proportion of superficial and parabasal cells). For study inclusion, study participants would have no greater than 5 percent superficial cells on a vaginal smear at baseline. The primary

efficacy analysis should show a statistically significant increase in superficial cells and a statistically significant decrease in parabasal cells.

- The mean change from baseline to week 12 in vaginal pH. For study inclusion, study participants should have a vaginal pH > 5.0 at baseline. The primary efficacy analysis should show a statistically significant lowering of vaginal pH.

- The mean change from baseline to week 12 in the moderate to severe self-assessed symptom identified by the subject as being the most bothersome to her. For study inclusion, study participants would have self-identified at least one moderate to severe vulvar and vaginal atrophy symptom. The primary efficacy analysis should show statistically significant improvement in the moderate to severe symptom identified by the subject as most bothersome. The recommended subject self-assessed symptoms of vulvar and vaginal atrophy include:

    1. Vaginal dryness (categorized as none, mild, moderate or severe).
    2. Vaginal and/or vulvar irritation/itching (categorized as none, mild, moderate or severe).
    3. Vaginal pain associated with sexual activity (categorized as none, mild, moderate or severe).
    4. Vaginal bleeding associated with sexual activity (categorized as none, mild, moderate or severe).

For numbers 3 and 4 listed above, the subject would also be able to indicate that, due to the absence of sexual activity in the reporting period, the symptom could not be assessed (NA = not applicable).

6.1.3 Study Design

The primary objective of Phase 3b Study 0713S5-413-NA was to evaluate the efficacy of 2 low-dose PVC regimens in the treatment of atrophic vaginitis at week 12.

The secondary objectives of Study 0713S5-413-NA were to evaluate:

1. The change from baseline in the vaginal maturation index (VMI) at weeks 4, and 6, and 52.
2. The effects of both PVC regimens on symptom relief, as assessed by a weekly symptom composite score through 12 weeks.
3. The effects of both PVC regimens on Genital Health Clinical Evaluation (GHCE) at weeks 4, 6, 12, and 52.
4. Endometrial safety at 52 weeks.

This outpatient, multicenter, double-blind, randomized, placebo-controlled, Phase 3b clinical trial was conducted at 49 sites in Canada and the United States. Enrollment ranged from no

subjects enrolled (7 sites) to 36 subjects per site. Per the protocol, subjects withdrawn from the study were not replaced regardless of the reason for withdrawal.

A total of 431 subjects met the inclusion and exclusion criteria at screening. Of these, 423 were randomly assigned to 1 of 4 treatment groups (2 active and 2 matching placebo), and 394 subjects completed the 12-week double-blind part of the study.

Each subject was instructed to complete the symptom diary each day during the entire screening period. Screening was expected to last 3 weeks. For some subjects, it required up to 7 weeks. Screening tests and procedures were completed and evaluated, and eligible subjects were randomly assigned to a treatment group and study medication was dispensed.

Subjects returned to the clinic site at week 4 (study day 28 ± 4), week 6 (study day 42 ± 4), week 12 (day 84 ± 4), week 26 (day 182 ± 7), and week 52 (day 365 ± 7).

The 12-week double-blind portion of Study 0713S5-413-NA was followed by a 40-week open-label period. During the 40-week open-label portion, all subjects, including those randomly assigned to placebo treatment groups received PVC treatment. Thus, subject initially randomized to placebo received PVC during the 40-week open-label period.

Inclusion Criteria:

Any subject who met the following inclusion criteria, as determined from assessments completed during screening, was eligible for study participation:

1. Generally healthy postmenopausal women aged 45 to 80 years, inclusive.
2. Signs and symptoms consistent with moderate to severe vaginal atrophy, defined as:
   a. baseline composite score (at initial screening visit) of at least 5 (1 = mild, 2 = moderate, 3 = severe) for the symptoms of vaginal dryness, itching/burning, and dyspareunia,
   b. total score of ≤ 15 on the GHCE,
   c. vaginal pH of ≥ 5.0.
3. Clinical diagnosis of atrophic vaginitis, defined as 0% to 5% superficial cells on the vaginal cytological smear.
4. Intact uterus.
5. Last natural (without exogenous hormone therapy) menstrual cycle completed at least 12 consecutive months before screening with serum estradiol concentration ≤ 30 pg/mL (≤ 110 pmol/L), and a serum follicle-stimulating hormone (FSH) level greater than the lower limit for postmenopausal women for the given laboratory.
6. Endometrial double-wall thickness < 5 mm, as determined by transvaginal ultrasound (TVU) of the uterus.
7. In the opinion of the investigator, the subject has a high probability for compliance with completion of the study.

Medical Officer's Comments:

For Study 0713S5-413-NA, the Applicant utilized an inclusion criterion for pH of ≥ 5 rather then the recommended >5. Per the Applicant, "the color indicator on the pH tape dispensers Wyeth is using for this study is for pH readings of 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, or 7.5. If we change the pH inclusion to > 5.0, patient with a vaginal reading of 5.1 or 5.2 will probably be recorded as 5.0 and they will not be eligible to enter the study. Only patients with a reading of 5.5 or greater will be eligible."

Because of the Applicant's explanation as stated above, this reviewer concurs with the use of a vaginal pH of ≥ 5 as an inclusion criterion for Study 0713S5-413-NA. Overall, the inclusion criteria utilized in Study 0713S5-413-NA are appropriate.

Exclusion Criteria:

1. Known or suspected estrogen-dependent neoplasia.
2. Endometrial proliferation, hyperplasia, malignancy at screening, or had undergone an endometrial ablation.
3. Any prior or current malignancy, with the exception of a history of basal cell carcinoma of the skin.
4. History of cerebrovascular accident, stroke, or transient ischemic attack.
5. History of neuro-ocular disorders (retinal thrombosis).
6. Known hypersensitivity to estrogens, progestins, or other ingredients of PVC.
7. History of myocardial infarction, ischemic heart disease, lipid disorder, or congestive heart failure (subjects with controlled lipid disorder can be enrolled).
8. Chronic renal or hepatic disease.
9. Known gallbladder disease (subjects who have had a cholecystectomy may be enrolled).
10. Use of any estrogen-, progestin-, or androgen-containing medication within 8 weeks before the initial screening visit for oral, vaginal, or transdermal therapy, and 6 months before screening for other treatment routes.
11. Use of vaginal moisturizers, lubricants, jellies, ointments, douches, herbal medications, over-the-counter preparations, home remedies, or natural estrogen products (for example, soy products) for the treatment of symptoms referable to vaginal atrophy or menopause within 7 days before the initial screening.
12. Use of Intrauterine Device (IUD) within 3 months before initial screening.
13. History or presence of clinically important hypertension or elevated supine blood pressure (>160 mm Hg systolic or > 90 mm Hg diastolic). Subjects who are effectively stabilized (< 160 mm Hg systolic or < 90 mm Hg diastolic) on 2 or fewer hypertension medications are permitted in the study.
14. Fasting triglycerides > 300 mg/mL (3.39 mmol/L) at the screening evaluation (subject can be treated and re-screened, see below).
15. Endocrine disease, except for controlled diabetes mellitus (glycosylated hemoglobin [HbA_{1c}] = 7) and controlled thyroid disease.
16. Prior or current thrombophlebitis, thrombosis, or thromboembolic disorder.
17. Known or suspected pregnancy.
18. Undiagnosed abnormal genital bleeding.
19. Evidence of malignant or premalignant changes on the prestudy mammogram.

20. Urogynecologic surgery within 3 months before the initial screening evaluation.
21. Current urogynecologic abnormalities or disorders that may prevent accurate evaluation of the study parameters.
22. Untreated vaginal infections (subject could be treated and re-screened).
23. Vaginitis at the initial screening evaluation other than that caused by estrogen deficiency.
24. Cervical cytologic smear (Papanicolaou [Pap] smear) report of atypical cells of undetermined significance [ASCUS]), squamous intraepithelial lesion (SIL), cervical intra-epithelial neoplasia (CIN), or any reported dysplasia at screening.
25. Clinically significant abnormal liver function test results at screening (> 1.5 times the upper limit of normal for the laboratory used).
26. Known positive for Human Immunodeficiency virus or Hepatitis B or C status.
27. Known alcohol or drug abuse.
28. Use of any investigational drug or device within 30 days before the initial screening visit.
29. Current tobacco use, or if former smoker, quit smoking within the year prior to the administration of the first dose of test article.

Subjects who were diagnosed with an exclusionary condition during screening could have been re-screened if their condition was medically managed within a reasonable period of time (for example, vaginal infection and hyperlipidemia).

Medical Officer's Comments:

Overall, the exclusion criteria utilized in Study 0713S5-413-NA are appropriate.

Permitted Concomitant Therapy:

1. Short-term treatments for allergies, colds, or flu.
2. Vitamin and mineral supplements.
3. Not more than 2 antihypertensive medications per day.
4. Other prior, non-excluded medications with established regimens.
5. Short-term treatment of an acute condition during the study, provided that it does not interfere with data interpretation.

Prohibited therapy:

1. Chronic use (> 10 days) of intravenous or oral steroids.
2. Any estrogens, androgens, or progestins, other than study medication.
3. Selective estrogen receptor modulators (SERMs).
4. Preparations used for the treatment of symptoms referable to vaginal atrophy or menopause if used within 7 days before screening: vaginal moisturizers, lubricants, jellies, ointments, douches, herbal medications, over-the-counter preparations, home remedies, or natural estrogen products (for example, soy products).
5. Any other investigational drug.

The study medication was administered as follows:

- A1 = PVC 21/7 days; 0.3 mg (0.5 gram) PVC daily for 21 days, then 7 days off
- A2 = Placebo 21/7 days; 0.5 gram placebo cream daily for 21 days, then 7 days off
- B1 = PVC 2x/wk; 0.3 mg (0.5 gram) PVC twice weekly (Monday and Thursday)
- B2 = Placebo 2x/wk; 0.5 gram placebo cream twice weekly (Monday and Thursday)

Cream Product	Strength	Formulation Number	Batch Number	Manufacturing Location
Double-Blind Period				
PVC	0.625 mg/g	0932158M	2005B0099	Rouses Point
Placebo Cream	----------	0932159M	2005B0098	Rouses Point
Open-Label Period				
PVC	(b) (4)		B17423 B233377 B38232 B44635	

Study medication for the double-blind period included: graduated reusable applicators for vaginal administration and 3 tubes containing 8 grams of either PVC or placebo cream. Each subject received blinded study medication on days 1 and 42.

Study medication for the open-label period included: graduated applicators for vaginal administration and PVC in 42.5 gram tubes (commercial package). On day 84, at the start of the open-label period, each subject received a sufficient number of 42.5 gram tubes to last approximately 100 days. On day 182, each subject was given a sufficient number of 42.5 gram tubes for the last 6 months of the study.

Procedures for monitoring treatment compliance included drug accountability, review of diary cards, and verbal information. Compliance was estimated as the ratio;

$$\frac{\text{actual total number of days on which cream was applied}}{\text{treatment interval}}$$

For the double-blind period, the treatment interval begins on the date on which the subject was randomly assigned to a treatment group through the week 12 visit date or the termination date for subjects withdrawing before week 12. For the entire study, data were collected through the week 52 visit date or the termination date for subjects withdrawing before week 52.

The primary efficacy analysis was conducted only at the completion of the double-blind period of Study 0713S5-413-NA. To be eligible for this efficacy evaluable population, a subject had to have taken test article on at least 3 of 7 of all double-blind days for the 21/7-treatment regimen, and between 1 of 7 and 3 of 7 of all double-blind days for the 2x/wk treatment regimen.

Vaginal Maturation Index:

A vaginal smear from the lateral vaginal wall was obtained to determine the percentages of parabasal, intermediate, and superficial cells during the screening visit and at weeks 4, 6, 12, and 52 (or at the final visit [week 52 or early termination]).

Vaginal pH:

A vaginal pH measurement was obtained as a part of the Genital Health Clinical Evaluation (GHCE) during the screening visit and weeks 4, 6, 12, and final visit. In conducting the GHCE, the investigator assessed the following parameters: vaginal pH, fluid secretion, epithelial mucosa, moisture, vaginal rugosity, and mucosa color.

Symptom Assessment:

The severity of symptoms associated with atrophic vaginitis was collected during screening and daily through week 12 on a daily diary card. Vaginal symptoms assessed included vaginal dryness, itching, burning, and dyspareunia and subjects were to score each of these symptoms every day. The scores were: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 5 = not applicable and 9 = not done. Weekly symptoms scores were derived from the average of all daily scores recorded during a 7-day period (excluding scores of 5 = not applicable and 9 = not done). At screening the subjects were to identify which of the 4 listed symptoms was the most bothersome to her. This self-identified most bothersome symptom was used to define 1 of the 3 co-primary endpoints of Study 0713S5-413-NA.

Statistical and Analytical Plans:

Per the submission, the efficacy analyses were conducted on the modified intent-to-treat (MITT) and efficacy evaluable (EE) populations. The MITT population was defined as all subjects who were randomly assigned, had at least 1 dose of test article, and a baseline and at least 1 follow-up value for the particular efficacy variable. The EE population was defined as all MITT subjects with no significant protocol violations. The efficacy data were summarized using the observed cases as well as a last-observation-carried-forward (LOCF) population. Per the statistical analysis plan, the primary analysis was based on the LOCF data from the MITT population at week 12. The safety population consisted of all randomly assigned subjects who applied at least 1 dose of test article.

The hypothesis testing was done for indices of VMI (superficial and parabasal cells), vaginal pH, and most bothersome symptom with an analysis of covariance (ANCOVA) with treatment and study center as factors, the baseline value as covariate, and the change from baseline as the dependent variable. ANCOVAs were calculated independently for each study collection period. Two (2) pairwise comparisons were made: 1 between each of the 2 active treatment groups and its corresponding placebo group. A mixed-effects model was also used to assess the weekly most bothersome symptom. This model included the terms week, treatment group, and week-by-treatment interaction as factors. Additionally, this model was used to look at changes over time in the individual symptom scores.

There was no adjustment for multiple primary endpoints, per the sponsor, because the study objective required significance for each endpoint. There was also no adjustment for multiple treatment group comparisons since each active treatment group had its own placebo group.

For the primary endpoint of vaginal maturation index, the sponsor assumed a mean difference and standard deviation (SD) of at least 8% ± 9% for superficial cells between each PVC group and its corresponding placebo group. It was estimated that there would be approximately 99% power, for this primary endpoint, with 110 evaluable subjects in each PVC treatment group and 55 subjects in each placebo group (alpha = 0.05, two-sided). For the vaginal pH primary endpoint and the most bothersome symptom primary endpoint, the sponsor assumed that the 110 evaluable subject estimate would provide approximately 85% and 96% power, respectively, assuming a mean difference and SD of at least 0.5 (1.5) and 0.5 (0.8), respectively.

The original statistical analysis plan specified that an unstructured covariance matrix would be used for the mixed effect model on the changes in vaginal symptoms over time. Per the submission, this model did not converge and an auto-regressive-1 model was used as an alternative. In the original protocol, the statistical analysis plan specified that compliance should be estimated by the ratio of the total number of days of test article application to the expected number of days of test article application. That is, if a subject in the 2x/wk treatment groups received 2 applications in a week, she would be 100% compliant. However, the sponsor indicates that compliance was actually estimated by the ratio of the total number of days with test article application to the total number of days in the study. Thus, the criteria fThe general reasons or compliance varied by regimen. Acceptable compliance was defined as a ratio between 1/7 and 3/7 for the 2x/wk regimen and a ratio of at least 3/7 for the 21/7 regimen.

6.1.4 Efficacy Findings

For the treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) due to menopause, the Agency's January 2003 draft Guidance for Industry entitled, "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation" recommends that one or more 12-week, randomized, double-blind, placebo-controlled clinical trials be conducted that evaluate the following three co-primary endpoints:

- The mean change from baseline to week 12 in the vaginal maturation index (proportions of superficial and parabasal cells). For study inclusion, study participants would have no greater than 5 percent superficial cells on a lateral-wall vaginal smear at baseline. The primary analysis should show a statistically significant increase in superficial cells and a statistically significant decrease in parabasal cells.

- The mean change from baseline to week 12 in vaginal pH. For study inclusion, study participants should have a vaginal pH > 5.0 at baseline. The primary analysis should show a statistically significant lowering of vaginal pH.

- The mean change from baseline to week 12 in the moderate to severe self-assessed symptom identified by the subject as being the most bothersome to her. For study inclusion, study participants would have self-identified at least one moderate to severe vulvar and vaginal atrophy symptom. The primary efficacy analysis should show statistically significant improvement in the moderate to severe symptom identified by the subject as most bothersome. The recommended subject self-assessed symptoms of vulvar and vaginal atrophy include:

  1. Vaginal dryness (categorized as none, mild, moderate or severe)
  2. Vaginal and/or vulvar irritation/itching (categorized as none, mild, moderate or severe).
  3. Vaginal pain associated with sexual activity (categorized as none, mild, moderate or severe).
  4. Vaginal bleeding associated with sexual activity (categorized as none, mild, moderate or severe).

For numbers 3 and 4 listed above, the subject would also be able to indicate that, due to the absence of sexual activity in the reporting period, the symptom could not be assessed (NA = not applicable).

Disposition of Subjects:

In Study 07135S-413-NA, a total of 742 subjects were screened for participation. Of this number, 431 were determined to be eligible for participation and were randomly assigned to treatment groups. Per the submission, 8 of the 431 randomly assigned subjects did not take any study medication or did not return to the clinic so that use of study medication could not be verified. These 8 subjects were not included in the safety population: 2 of these 8 subjects were assigned to PVC 21/7, 1 to PVC 2x/wk, and 5 to placebo 2x/wk. Therefore, a total of 423 subjects who applied test article at least once make up the safety population. Of these 423 subjects, 394 (93.1%, 394 of 423 treated subjects) completed the double-blind period of Study 0713S5-413-NA (129 subjects in the PVC 21/7 treatment group, 69 subjects in the placebo 21/7 treatment group, 132 subjects in the PVC 2x/wk treatment group, and 64 subjects in the placebo 2x/wk treatment group). Of these 394 subjects, 344 subjects completed the study through week 52 (229 subjects received PVC for both the double-blind and open-label periods and 115 subjects received placebo treatment in the first 12 weeks and then received PVC treatment during the last 40 weeks of the study). Fifty (50) subjects discontinued participation in the open-label period before week 52.

The general reasons for discontinuing Study 0713S5-413-NA are listed in Table 2.

Table 2: Number (Percent) of Subjects Discontinuing by Study Period, Reason, and Treatment

Study Period	**Treatment Sequence**				
	PVC 21/7	Placebo 21/7	PVC 2x/wk	Placebo 2x/wk	Total
Double-Blind					
Safety Population (%)	n=143 (100)	n=72 (100)	n=140 (100)	n=68 (100)	n=423 (100)

Completed Double-Blind	129 (90.2)	69 (95.8)	132 (94.3)	64 (94.1)	394 (93.1)
Discontinued	14 (9.8)	3 (4.2)	8 (5.7)	4 (5.9)	29 (6.9)
Adverse Event	6 (4.2)	1 (1.4)	4 (2.9)	2 (2.9)	13 (3.1)
Lost to Follow-Up	1 (0.7)	0	0	1 (1.5)	2 (0.5)
Protocol Violation	1 (0.7)	0	1 (0.7)	0	2 (0.5)
Subject Request	6 (4.2)	2 (2.8)	3 (2.1)	1 (1.5)	12 (2.8)
Open Label Safety Population (%)	129 (90.2)	69 (95.8)	132 (94.3)	64 (94.1)	394 (93.1)
Completed Open-Label	110 (85.3)	60 (87.0)	119 (90.2)	55 (85.9)	344 (87.3)
Discontinued	19 (14.7)	9 (13.0)	13 (9.8)	9 (14.1)	50 (12.7)
Adverse event	2 (1.6)	1 (1.4)	6 (4.5)	4 (6.3)	13 (3.3)
Lost to Follow-Up	10 (7.7)	2 (2.9)	5 (3.7)	3 (4.7)	20 (5.1)
Protocol Violation	1 (0.8)	1 (1.4)	1 (0.8)	0	3 (0.8)
Subject Request	6 (4.7)	5 (7.2)	1 (0.8)	2 (3.1)	14 (3.6)

Source: Modified Table 8-1: Number (%) of Subjects Discontinuing by Study Phase, Reason, and Treatment; 4-Month Safety Update received January 15, 2008.
PVC = Premarin® Vaginal Cream; PVC 21/7 = apply PVC daily for 21 days, then 7 days off; PVC 2x/wk = apply PVC twice a week.

Of the 29 subjects (6.9%, 29 of 423 subjects) who discontinued during the double-blind period of Study 0713S5-413-NA, 13 subjects (6.9%) discontinued for adverse events and 12 (2.8%) at the subject's request. Fifty (50) of the 394 subjects (12.7%) who entered the open-label period of Study 0713S5-413-NA withdrew from the study. The most common reasons were lost to follow-up (20 subjects, 5.1%), subject request (14 subjects, 3.6%), and adverse events (13 subjects, 3.3%). Discontinuations for adverse events are presented in more detail in subsection 7.1.3.2 Adverse events associated with dropouts on page 57 of this review.

During the double-blind period of Study 0713S5-413-NA, two subjects were withdrawn because of protocol violations: Subject (b) (6) (ASCUS at screening) in the PVC 21/7 treatment group and Subject (b) (6) (did not meet the GHCE score criteria) in the PVC 2x/wk treatment group.

During the open-label period of Study 0713S5-413-NA, three subjects were withdrawn because of protocol violations: Subject (b) (6) (non-compliant), Subject (b) (6) (prohibited medication), and Subjec (b) (6) (verbatim: "husband passed away forgot to put medication").

Medical Officer's Comments:

Overall, the percentage of subjects discontinuing due to an adverse event during Study 0713S5-413-NA was small (3.1%; 13 of 423 treated subjects during the double-blind phase and 3.3%, 13 of 394 treated subjects during the open-label phase). However, the PVC 21/7 treatment group reported more discontinuations than the PVC 2x/wk treatment group during both phase of Study 0713S5-413-NA.

Thirty-nine (39) subjects had protocol violations or deviations, but continued in Study 0713S5-413-NA. A summary of violations and deviations is shown in Table 3.

Table 3: Number of Subjects with Protocol Violations and/or Deviations

Violation or Deviation Period	n[a]	Excluded From Some EE Analyses
Screening and Double-Blind		
Over and under compliance with study medication administration	11	X[b]
Greater than 5% superficial cells on the VMI smear	5	X
Use of excluded mediation that could interfere with interpretation of results	3	X
Use of excluded medication that was thought not to interfere with interpretation of results	3	
Screening pap smear showed ASCUS	3	
Abnormal baseline mammogram	2	
History of thromboembolic event or disorder	2	
Hypertension during the screening period	2	
No waiver for endometrial biopsy, insufficient tissue	2	
Vaginal pH did not meet entry criteria	2	X
Physical examination not performed at visit 5	1	
Took different regimen than what was assigned	1	
Screening visit window greater than 7 weeks	1	
Age < 45	1	
Failed screening GHCE	1	
Open-Label		
Endometrial biopsy not performed at week 52	1	N/A
Noncompliance	1	N/A
Use of excluded medication that could interfere with interpretation of results	1	N/A
Use of excluded medication that was thought not to interfere with interpretation of results	1	N/A

Source: Modified Table 8-2: Number of Subjects With Protocol Violations and/or Deviations; 4-Month Safety Update received January 25, 2008.
EE = efficacy evaluable.
VMI = Vaginal maturation index.
ASCUS = atypical squamous cells of undetermined significance.
N/A = not applicable because EE analyses were not performed after the open-label period.
a. Total greater than number of subjects because some subjects had more than 1 violation or deviation.
b. Excluded from all efficacy endpoints.

Medical Officer's Comments:

The majority of protocol violations and/or deviations were related to relevant inclusion and exclusion criteria.

The following table shows the demographic characteristics for the ITT population in Study 0713S5-413-NA.

Table 4: Summary of Demographic and Baseline Characteristics: Safety Population

Characteristics	PVC 21/7 (n = 143)	Placebo 21/7 (n = 72)	PVC 2x/wk (n = 140)	Placebo 2x/wk (n = 68)	Total (n = 423)
Age (years)					
Mean ± (SD)	57.68 (5.79)	57.96 (5.76)	57.47 (5.45)	58.69 (5.81)	57.82 (5.68)
Range	44 - 77	47 – 74	45 – 75	47 – 77	44 – 77
Race, n (%)					
White	134 (93.7)	63 (87.5)	127 (90.7)	66 (97.1)	390 (92.2)
Other	9 (6.3)	9 (12.5)	13 (9.3)	2 (2.9)	33 (7.8)
Weight (kg)					
Mean ± (SD)	68.99 (15.32)	67.82 (15.04)	68.24 (12.40)	67.37 (10.06)	68.28 (13.56)
Range	44.00 – 132.81	40.20 – 122.47	46.80 – 107.50	46.27 – 99.30	40.20 – 132.81
(Missing)	(2)	(0)	(1)	(0)	(3)
Height (cm)					
Mean ± (SD)	161.55 (6.32)	160.90 (6.35)	161.54 (5.95)	162.22 (6.11)	161.54 (6.16)
Range	145.05 – 176.53	147.50 – 179.50	146.00 – 177.80	145.00 – 177.00	145.00 – 179.50
(Missing)	(2)	(0)	(1)	(0)	(3)
Years Since Last Period					
Mean ± (SD)	8.90 (5.95)	9.94 (6.69)	7.95 (5.84)	9.88 (6.70)	8.92 (6.20)
Range	0.45 – 27.34	0.98 – 30.01	0.59 – 31.16	1.11 – 31.43	0.45 – 31.43
(Missing)	(8)	(5)	(5)	(1)	(19)

Source: Modified Table 8-3: Summary of Demographic and Baseline Characteristics: Safety Population; 4-Month Safety Update received January 25, 2008.
PVC = Premarin® Vaginal Cream; PVC 21/7 = apply PVC daily for 21 days, then 7 days off; placebo 21/7 = apply placebo daily for 21 days, then 7 days off; PVC 2x/wk = apply PVC twice a week; placebo 2x/wk = apply placebo twice a week.
SD = Standard deviation.

Medical Officer's Comments:

There were no statistically significant differences among treatment groups for any demographic characteristics.

Measurements of Treatment Compliance:

Per the submission, compliance was estimated as the ratio of the total number of days with test article application to the total number of days in the double-blind phase of Study 0713S5-413-NA. Acceptable compliance was defined in the SAP as a ratio between 1/7 and 3/7 for the PVC 2x/wk dosing regimen and a ratio of at least 3/7 for the PVC 21/7 dosing regimen. Table 5 shows the number of subjects meeting these criteria.

Table 5: Summary of Compliance: Number (%) of Subjects in the Double-Blind Phase

Compliance	PVC 21/7 (n = 143)	Placebo 21/7 (n = 72)	PVC 2x/wk (n = 140)	Placebo 2x/wk (n = 68)	Total (n = 423)
Yes	139 (97.2)	69 (95.8)	136 (97.1)	68 (100.0)	412 (97.4)
No	4 (2.8)	3 (4.2)	4 (2.9)	0	11 (2.6)

Source: sNDA 20-216/SE2-060, Final Study Report, Table 9-2.
Abbreviations: PVC = Premarin Vaginal Cream; PVC 21/7 = apply PVC daily for 21 days and then 7 days of no therapy; placebo cream 21/7 = apply placebo cream for 21 days and the 7 days of no therapy; PVC 2x/wk = apply PVC twice a week, continuously; placebo cream 2x.wk = apply placebo cream twice a week, continuously

Medical Officer's Comments:

More than 95% of subjects met defined compliance in all treatment groups. Per the submission, the 11 subjects who did not meet the compliance criteria were included in the MITT population, but excluded from the EE population.

Data Quality Assurance:

To ensure that the data collected were accurate, consistent, complete, and reliable, a representative of Wyeth Pharmaceuticals made periodic visits to the investigational site while Study 0713S5-413-NA was in progress to check the accuracy and completeness of the data being entered. In addition, the case report forms (CRFs) were checked against the subject's source documents. Per the submission, data from the investigational site were reviewed and the investigator clarified any missing or contradictory data for all critical endpoints. The accuracy of the clinical database was verified through a series of reviews of data listings and other pertinent data processing reports.

Primary Analyses of Efficacy:

Population Analyzed:

Per the submission, the primary efficacy analyses were conducted at the end of the double-blind period (week 12) with the MITT population and an EE population. The MITT population is defined as all randomly assigned subjects who recorded at least 1 application of study medication and had a baseline value and at least 1 follow-up value for that variable. The efficacy evaluable (EE) population is defined as all subjects who meet all requirements for the MITT population plus no significant protocol violations. To be included in the EE population, per the submission, subjects must meet the following criteria:

"1. Superficial cells ≤ 5 percent on the baseline vaginal cytologic smear.
2. Did not take any other estrogen containing products during treatment period or other vaginal products that may interfere with efficacy of PVC.
.3. Dosing compliance – at least 3/7 of all double-blind days for daily arm, and between 1.7 and 3/7 of all double-blind days for twice weekly arm."

Medical Officer's Comments:

The MITT population to be analyzed, as described above, does not meet the following recommended inclusion criteria: vaginal pH > 5.0, superficial cells ≤ 5%, and self-identification of a moderate to severe symptom identified as most bothersome. The Applicant was requested to provide this information on November 15, 2007 and again on May 21, 2008.

In sNDA 20-216/SE2-060, a total of 130 subjects did not have baseline and/or any on-treatment data for the three co-primary endpoints and were not included in the MITT population. See Table 6.

Table 6: Number (Percent) of Subjects in the MITT Population Who did not Have Baseline and/or Any On-Treatment Data for the Primary Efficacy Analyses at Week 12

Primary Efficacy Endpoints	PVC 21/7 (n = 143)	Placebo 21/7 (n = 72)	PVC 2x/wk (n = 140)	Placebo 2x/wk (n = 68)	Total (n = 423)
VMI	1 (1.40)	1 (1.39)	1 (0.71)	0	4 (0.95
Vaginal pH	7 (4.90)	4 (5.56)	5 (3.57)	4 (5.88)	20 (4.73)
Most Bothersome Symptom	42 (29.37)	16 (22.22)	33 (23.57)	15 (22.06)	106 (25.06)

Source: Modified Table 9-1: Number (%) of Subjects Who did not Have Baseline and/or On-Therapy Data in the MITT Population; sNDA 20-216/SE2-060 submission dated September 25, 2007.
PVC = Premarin® Vaginal Cream; PVC 21/7 = apply PVC daily for 21 days, then 7 days off; placebo 21/7 = apply placebo daily for 21 days, then 7 days off; PVC 2x/wk = apply PVC twice a week; placebo 2x/wk = apply placebo twice a week
MITT = Modified intent-to-treat.
VMI = Vaginal maturation index.

Medical Officer's Comments:

As shown in Table 6, 30.7% (130 of 423 subjects) could not be included in the MITT analyses for the three co-primary endpoints, with the most bothersome symptom endpoint accounting for the majority of excluded subjects. Per the submission, most of the subjects who were not included in the most bothersome symptom endpoint were those subjects who reported painful intercourse as their most bothersome symptom, but listed "not applicable" for that symptom during the screening and/or treatment phases in Study 0713S5-413-NA.

Vaginal Maturation Index:

A vaginal smear from the lateral vaginal wall was obtained to determine the percentages of parabasal, intermediate, and superficial cells during the screening visit and at weeks 4, 6, 12, and 52 (or at the final visit [week 52 or early termination]). Per the submission, increases in the percentage of superficial cells and decreases in parabasal cells indicate a reduction in vaginal atrophy. The reported results for Study 0713S5-413-NA, included in the submission, are shown in Table 7 and Table 8.

Table 7: Change in Percentage of Superficial Cells at 12 Weeks: MITT Population, LOCF ANCOVA

			Raw Score Mean		Adj. Mean Change			
					Adj.		Within-	Between-

Week	Treatment Group	N	Mean	STD Dev.	Mean Change	STD Error	Group p-Value	Group p-Value
SCREENING	PVC 21/7	141	0.35	1.42				
	Placebo 21/7	71	0.92	3.81				
	PVC 2x/wk	139	0.76	4.54				
	Placebo 2x/wk	68	0.51	2.14				
WEEK 12	PVC 21/7	141	28.48	24.02	27.86	1.72	<.001	<.001
	Placebo 21/7	71	3.59	11.59	3.01	2.39	0.209	
	PVC 2x/wk	139	26.12	23.51	25.79	1.73	<.001	<.001
	Placebo 2x/wk	68	1.99	6.47	1.04	2.44	0.670	

Source: sNDA 20-216/SE2-060 submission dated September 25, 2007; Interim Report; Table 9-3; page 38.
Abbreviations: MITT = modified intent-to-treat; LOCF = last observation carried forward; ANCOVA = analysis of covariance with treatment and site as factors and baseline value as a covariate; PVC = Premarin® Vaginal Cream; PVC 21/7 = apply PVC for 21 days and then 7 days off; placebo 21/7 = apply placebo cream for 21 days and then 7 days off; PVC 2x/wk = apply PVC twice a week, continuously; placebo 2X/wk – apply placebo cream twice a week, continuously.

Table 8: Change in Percentage of Parabasal Cells at 12 Weeks: MITT Population, LOCF ANCOVA

			Raw Score Mean		Adj. Mean Change			
Week	Treatment Group	N	Mean	STD Dev.	Adj. Mean Change	STD Error	Within-Group p-Value	Between-Group p-Value
SCREENING	PVC 21/7	141	62.70	43.66				
	Placebo 21/7	71	60.56	42.98				
	PVC 2x/wk	139	59.53	45.36				
	Placebo 2x/wk	68	63.90	42.67				
WEEK 12	PVC 21/7	141	0.39	2.61	-60.63	2.15	<.001	<.001
	Placebo 21/7	71	38.87	42.86	-21.52	2.98	<.001	
	PVC 2x/wk	139	1.94	11.79	-58.23	2.16	<.001	<.001
	Placebo 2x/wk	68	54.78	42.91	-6.63	3.05	0.030	

Source: sNDA 20-216/SE2-060 submission dated September 25, 2007; Interim Report; Table 9-4; page 39.
Abbreviations: MITT = modified intent-to-treat; LOCF = last observation carried forward; ANCOVA = analysis of covariance with treatment and site as factors and baseline value as a covariate; PVC - Premarin® Vaginal Cream; PVC 21/7 = apply PVC for 21 days and then 7 days off; placebo 21/7 = apply placebo cream for 21 days and then 7

days off; PVC 2x/wk = apply PVC twice a week, continuously; placebo 2X/wk – apply placebo cream twice a week, continuously.

On May 21, 2008, the Applicant was requested to provide data for superficial and parabasal cells for the study population who, at baseline, met the following three inclusion criteria: vaginal pH ≥ 5.0, superficial cells ≤ 5%, and self-identification of a moderate to severe symptom identified as most bothersome. This information is presented in Table 9.

Table 9: Summary Tabulation of Superficial and Parabasal Cells at Week 12, LOCF

			Baseline			Adjusted Mean Change		
Tests	Week	Treatment Group	N	Mean	Standard Deviation	Adj. Mean Change	Standard Deviation	p-value
Parabasal Cells	Week 12	PVC 21/7	92	63.8	44.1	-61.72	2.76	<.001
		Placebo 21/7	50	56.5	43.5	-21.73	3.69	
		PVC 2x/wk	98	60.2	45.1	-58.41	2.69	<.001
		Placebo 2x/wk	48	61.5	43.5	-8.93	3.85	
Superficial Cells	Week 12	PVC 21/7	92	0.33	1.24	23.68	2.03	<.001
		Placebo 21/7	50	0.70	1.75	4.69	2.73	
		PVC 2x/wk	98	0.20	0.99	28.35	1.98	<.001
		Placebo 2x/wk	48	0.42	1.40	1.20	2.83	\

Source: Table 1-1 provided on May 27, 2008.
LOCF = Last observation carried forward.
Abbreviations = PVC = Premarin® Vaginal Cream; PVC 21/7 = apply PVC daily for 21 days, then 7 days off; placebo 21/7 = apply placebo daily for 21 days, then 7 days off; PVC 2x/wk = apply PVC twice a week; placebo 2x/wk = apply placebo twice a week

Medical Officer's Comments:

Based on the reported mean change in the proportion of superficial cells and parabasal cells between baseline and week 12, treatment with 0.3 mg (0.5 gram) of PVC 21/7 and 0.3 mg (0.5 gram) of PVC 2x/wk statistically increased the mean percentage of superficial cells from baseline to week 12 ($p < 0.001$ for both) and statistically decreased the mean percentage of parabasal cells from baseline to week 12 ($p < 0.001$) compared to placebo in both the MITT population and in the modified MITT population who, *at baseline, met the following three inclusion criteria: vaginal pH ≥ 5.0, superficial cells ≤ 5%, and self-identification of a moderate to severe symptom identified as most bothersome.*

Per the Statistical Reviewer, the "treatment effects were also statistically significant ($p<0.001$) for the increase in percentage of superficial cells at Week 12 and for the decrease in parabasal cells at Week 12. These results are from analyses of 419 subjects with follow-up assessments of

superficial and parabasal cells, and are adjusted for study site and for baseline values of parabasal or superficial cells. The increase in superficial cells for the active treatment groups was approximately 24 percentage units greater than the increase observed for the matching placebo groups. The decrease in parabasal cells was approximately 40 percentage units greater for PVC 21/7 than for Placebo 21/7, and about 50 units greater for PVC 2x/wk than for Placebo 2x/wk."

The Statistical Reviewer was "able to reproduce these analyses and generate the results found in the submission."

Vaginal pH:

A vaginal pH measurement was obtained as a part of the Genital Health Clinical Evaluation (GHCE) during the screening visit and weeks 4, 6, 12, and 52 (or at the time of early discontinuation). In conducting the GHCE, the investigator assessed the following parameters: vaginal pH, fluid secretion, epithelial mucosa, moisture, vaginal rugosity, and mucosa color. The GHCE parameters were scored. Each subject needed a total GHCE score of ≤ 15 to be eligible for enrollment. The GHCE score was derived from the sum of all parameters. If a single parameter was missing, the GHCE score was not calculated.

Medical Officer's Comments:

For Study 0713S5-413-NA, the Applicant utilized an inclusion criterion for pH of ≥ 5 rather then the recommended >5. Per the Applicant, "the color indicator on the pH tape dispensers Wyeth is using for this study is for pH readings of 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, or 7.5. If we change the pH inclusion to > 5.0, patient with a vaginal reading of 5.1 or 5.2 will probably be recorded as 5.0 and they will not be eligible to enter the study. Only patients with a reading of 5.5 or greater will be eligible."

The reviewer concurs with the use of a vaginal pH of ≥ 5 as an inclusion criterion.

In the September 1, 2005 letter from DRUP, Wyeth Pharmaceuticals was advised that no results of the GHCE "investigator measurement would be considered in determining the effectiveness of the drug product and no findings from the GHCE would appear in labeling."

The effect of treatment on vaginal pH is presented in Table 10.

Table 10: Changes in Vaginal pH at 12 weeks: MITT Population, LOCF ANCOVA

			Raw Score Mean		Adj. Mean Change			
					Adj.		Within-	Between-

Week	Treatment Group	N	Mean	STD Dev.	Mean Change	STD Error	Group p-Value	Group p-Value
SCREENING	PVC 21/7	136	6.72	0.75				
	Placebo 21/7	68	6.58	0.68				
	PVC 2x/wk	135	6.54	0.79				
	Placebo 2x/wk	64	6.67	0.76				
WEEK 12	PVC 21/7	136	5.03	0.68	-1.62	0.07	<.001	<.001
	Placebo 21/7	68	6.27	0.97	-0.36	0.10	<.001	
	PVC 2x/wk	134	5.02	0.77	-1.57	0.07	<.001	<.001
	Placebo 2x/wk	64	6.41	0.99	-0.26	0.10	0.008	

Source: sNDA 20-216/SE2-060 submission dated September 25, 2007; Interim Report; Table 9-5; page 41.
Abbreviations: MITT = modified intent-to-treat; LOCF = last observation carried forward; ANCOVA = analysis of covariance with treatment and site as factors and baseline value as a covariate; PVC = Premarin® Vaginal Cream; PVC 21/7 = apply PVC for 21 days and then 7 days off; placebo 21/7 = apply placebo cream for 21 days and then 7 days off; PVC 2x/wk = apply PVC twice a week, continuously; placebo 2X/wk – apply placebo cream twice a week, continuously.

On May 21, 2008, the Applicant was requested to provide data for vaginal pH for the study population who, at baseline, met the following three inclusion criteria: vaginal pH ≥ 5.0, superficial cells ≤ 5%, and self-identification of a moderate to severe symptom identified as most bothersome. On May 27, 2008 the Applicant provided the information requested. This information is presented in Table 11.

Table 11: Summary Tabulation of Vaginal pH at Week 12: LOCF

		Baseline			Adjusted Mean Change		
Week	Treatment Group	N	Mean	Standard Deviation	Adj. Mean Change	Standard Deviation	p-value
Week 12	PVC 21/7	91	6.71	0.72	-1.55	0.09	<.001
	Placebo 21/7	48	6.50	0.70	-0.49	0.12	
	PVC 2x/wk	96	6.50	0.79	-1.63	0.09	<.001
	Placebo 2x/wk	47	6.69	0.81	-0.24	0.12	

Source: Table 1-2 provided on May 27, 2008.
LOCF = Last observation carried forward.
Abbreviations = PVC = Premarin® Vaginal Cream; PVC 21/7 = apply PVC daily for 21 days, then 7 days off; placebo 21/7 = apply placebo daily for 21 days, then 7 days off; PVC 2x/wk = apply PVC twice a week; placebo 2x/wk = apply placebo twice a week

Medical Officer's Comments:

Based on the reported vaginal pH results in Phase 3b Study 0713S5-413-NA, both dosing regimens (0.3 mg [0.5 gram] PVC 21/7 and 0.3 mg [0.5 gram] PVC 2x/wk) were effective in demonstrating a statistically significant reduction in vaginal pH between baseline and week 12 compared to placebo in both the MITT population and in the modified MITT population who, *at baseline, met the following three inclusion criteria: vaginal pH ≥ 5.0, superficial cells ≤ 5%, and self-identification of a moderate to severe symptom identified as most bothersome..*

Per the Statistical Reviewer, the "applicant reported statistically significant reductions (p<001) in vaginal pH for each active treatment group versus its placebo group. The average reduction in vaginal pH for each active treatment group was approximately 1.6 compared with 0.3 for each placebo treatment group. The means, which are adjusted for study site and for vaginal pH at baseline, are from analyses of 402 subjects with a follow-up assessment of vaginal pH."

The Statistical Reviewer was "able to reproduce these analyses and generate the results found in the submission."

Most Bothersome Vulvar and Vaginal Atrophy Symptom:

In Study 0713S5-413-NA, each subject self administered a questionnaire at screening and classified the severity (none, mild, moderate, or severe) of the following four symptoms; vaginal dryness, vaginal itching, vaginal burning, or painful intercourse. In addition, the subject was asked to identify one of these four symptoms that was most bothersome to her. Subjects maintained a daily diary to record symptoms and study medication administration for the first 12 weeks of Study 0713S5-413-NA. For weeks 13 thru 52, the subject only recorded daily study drug administration.

In the sNDA 20-216/SE2-060 submission received on September 25, 2007, a total of 412 subjects (97.4%, 412 of 423 randomized subjects) identified a most bothersome symptom at baseline. The data demonstrates that painful intercourse was the symptom identified as most bothersome by the largest number of subjects followed by vaginal dryness. See Table 12.

Table 12: Summary of the Symptom Selected as the Most Bothersome Symptom at Baseline by Number (%) of Subjects and Treatment

	Treatment			
Symptom	PVC 21/7 n = 138	Placebo 21/7 n = 70	PVC 2x/wk n = 137	Placebo 2x/wk n = 67
Vaginal Dryness	34 (24.64)	21 (30.00)	32 (23.36)	16 (23.88)
Vaginal Itching	7 (5.07)	11 (15.71)	12 (8.76)	9 (13.43)
Vaginal Burning	9 (6.52)	5 (7.14)	10 (7.30)	5 (7.46)
Painful Intercourse	88 (63.77)	33 (47.14)	83 (60.58)	37 (55.22)

Source: sNDA 20-216/SE2-060 submission dated September 25, 2007; Interim Report; Table9-6; page 42.
Abbreviations: PVC = Premarin® Vaginal Cream; PVC 21/7 = apply PVC for 21 days and then 7 days off; placebo 21/7 = apply placebo cream for 21 days and then 7 days off; PVC 2x/wk = apply PVC twice a week, continuously; placebo 2X/wk – apply placebo cream twice a week, continuously.

Per the submission, symptoms were scored as follows: none = 0, mild = 1, moderate = 2, and severe = 3. A change in the symptom score between baseline and week 12 was presented in the submission for a composite score of all symptoms identified as most bothersome. A composite score is shown in Table 13.

Table 13: Change in the Most Bothersome Symptom Score During the Double-Blind Phase of Study 0713S5-413-NA: MITT Population, LOCF ANCOVA

			Raw Score Mean		Adj. Mean Change			
Week	Treatment Group	N	Mean	STD Dev.	Adj. Mean Change	STD Error	Within-Group p-Value	Between-Group p-Value
BASELINE	PVC 21/7	101	2.01	1.03				
	Placebo 21/7	56	2.17	0.82				
	PVC 2x/wk	107	2.22	0.78				
	Placebo 2x/wk	53	2.05	1.00				
WEEK 12	PVC 21/7	101	0.76	1.05	-1.27	0.10	<.001	0.001
	Placebo 21/7	56	1.41	1.08	-0.75	0.13	<.001	
	PVC 2x/wk	107	0.80	0.87	-1.37	0.10	<.001	<.001
	Placebo 2x/wk	52	1.32	1.18	-0.72	0.14	<.001	

Source: sNDA 20-216/SE2-060 submission dated September 25, 2007; Interim Report; Table 9-7; page 46.
Abbreviations: MITT = modified intent-to-treat; LOCF = last observation carried forward; ANCOVA = analysis of covariance with treatment and site as factors and baseline value as a covariate; PVC = Premarin® Vaginal Cream; PVC 21/7 = apply PVC for 21 days and then 7 days off; placebo 21/7 = apply placebo cream for 21 days and then 7 days off; PVC 2x/wk = apply PVC twice a week, continuously; placebo 2X/wk – apply placebo cream twice a week, continuously.

Medical Officer's Comments:

As shown in Table 13, treatment with 0.3 mg (0.5 gram) PVC 21/7 and PVC 2x/wk significantly reduced the composite symptom score for the most bothersome symptom at week 12 relative to placebo. However, a composite symptom score analysis does not meet the recommendation of the Agency's 2003 draft clinical evaluation guidance for the moderate to severe self-assessed vaginal symptom identified as most bothersome co-primary endpoint:

- *Mean change from baseline to week 12 in the moderate to severe self-assessed symptom identified by the subject as being the most bothersome to her. The primary analysis should show statistically significant improvement in the moderate to severe symptom identified by the subject as most bothersome to her.*

On November 15, 2007, the Applicant was requested to provide an analysis of change from baseline to week 12 for each separate symptom (vaginal dryness, vaginal itching, vaginal burning, and painful intercourse) reported as moderate to severe and most bothersome at baseline. Subjects had to meet all three recommended co-primary endpoints to be included in the efficacy analysis:

1. Self-identified at least 1 moderate to severe vulvar and vaginal atrophy symptom that was also self-identified as most bothersome.

2. Had a baseline pH of ≥ 5.0.

3. Had no more than 5% superficial cells on a vaginal smear.

The following two tables were provided by the Applicant on December 13, 2007 and were also included in the 4-Month Safety Update.

Table 14: Summary Tabulation of Mean Weekly Symptom Change Score at Week 12 Among Subjects Who Satisfied all Co-Primary Endpoints, LOCF

	PVC 21/7 (n = 93)[a]		Placebo 21/7 (n = 51)[a]		PVC 2x/wk (n = 98)[a]		Placebo 2x/wk (n = 48)[a]	
Symptom	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Dyspareunia	50	-1.48 (1.17)	18	-0.40 (1.01)	52	-1.55 (0.92)	21	-0.62 (1.23)
Vaginal dryness	30	-1.31 (1.06)	19	-1.28 (1.21)	27	-1.40 (0.98)	15	-1.26 (1.08)
Vaginal itching	6	-0.63 (0.96)	9	-0.69 (0.76)	12	-0.99 (1.09)	8	-0.29 (0.84)
Vaginal burning	7	-0.54 (0.99)	5	-0.27 (0.93)	7	-1.23 (1.34)	4	-0.66 (1.68)

Source: Adapted from sNDA 20-216/SE2-060; requested information provided on December 13, 2007 and Table 9-8 included in the 4-Month Safety Update, page 48.
Abbreviations: LOCF = last observation carried forward; n = number of subjects satisfying all 3 inclusion criteria; PVC = 0.5 gram (0.3 mg) Premarin® Vaginal Cream; SD = standard deviation.
PVC 21/7 = apply PVC for 21 days and then 7 days off; placebo 21/7 = apply placebo cream for 21 days and then 7 days off; PVC 2x/wk = apply PVC twice a week, continuously; placebo 2X/wk = apply placebo cream twice a week, continuously.
[a] Total number of subjects equals the sum for the 4 symptoms because each subject has only 1 most bothersome symptom.

Table 15: Comparison of PVC Treatment With Placebo for the Adjusted Mean Change in the Most Bothersome Symptom Score from Baseline to Week 12: MITT Population, LOCF

Symptom	Adjusted Mean (SE)			Adjusted Mean (SE)		
	PVC 21/7 (n = 93)[a]	Placebo 21/7 (n = 51)[a]	p-Value[b]	PVC 2x/wk (n = 98)[a]	Placebo 2x/wk (n = 48)[a]	p-Value[c]
Dyspareunia	-1.52 (0.13)	-0.41 (0.22)	<.001	-1.49 (0.13)	-0.66 (0.21)	0.001
Vaginal dryness	-1.48 (0.17)	-1.11 (0.22)	0.189	-1.39 (0.18)	-1.16 (0.24)	0.441
Vaginal						

itching	-0.61 (0.38)	-0.59 (0.31)	0.975	-0.99 (0.27)	-0.42 (0.34)	0.196
Vaginal burning	-0.92 (0.40)	-0.23 (0.45)	0.276	-0.91 (0.40)	-0.60 (0.51)	0.633

Source: Source: Adapted from sNDA 20-216/SE2-060; requested information provided on December 13, 2007 and Table 9-9 included in the 4-Month Safety Update, page 48.
Abbreviations: LOCF = last observation carried forward; n = number of subjects satisfying all 3 inclusion criteria; PVC = 0.5 gram (0.3 mg) Premarin® Vaginal Cream; SE = standard error.
PVC 21/7 = apply PVC for 21 days and then 7 days off; placebo 21/7 = apply placebo cream for 21 days and then 7 days off; PVC 2x/wk = apply PVC twice a week, continuously; placebo 2X/wk = apply placebo cream twice a week, continuously.
ANCOVA = Analysis of covariance with baseline value as the covariate.
[a] Total number of subjects equals the sum for the 4 symptoms because each subject has only 1 most bothersome symptom.
[b] Comparison of PVC 21/7 with placebo 21/7.
[c] Comparison of PVC 2x/wk with placebo 2x/wk.

Medical Officer's Comments:

Per the Statistical Reviewer, the findings represented in Table 14 and Table 15 are unadjusted for study site as was specified in the statistical analysis plan.

The Statistical Reviewer re-analyzed the data and adjusted the means for study site and baseline value. The results of ANCOVA and summary of least-squared means (standard error) in the change from baseline at week 12 by each symptom reported as most bothersome symptom at baseline among the subgroup of subjects who had a baseline vaginal pH of ≥ 5.0, who had ≤ 5% superficial cells on a vaginal smear and whose most bothersome symptom was moderate to severe are shown in Table 16.

Table 16: Results of ANCOVA and Summary of Least-Squared Means (Standard Error) in the Change from Baseline at Week 12 by Each Symptom Reported as Most Bothersome Symptom at Baseline, MITT Population, LOCF ANCOVA

Symptom	Adjusted Mean (SE)					Adjusted Mean (SE)				
	PVC 21/7 (n = 93)[a]		Placebo 21/7 (n = 51)[a]		p-Value[b]	PVC 2x/wk (n = 98)[a]		Placebo 2x/wk (n = 48)[a]		p-Value[c]
	n	Mean (SE)	n	Mean (SE)		n	Mean (SE)	n	Mean (SE)	
Dyspareunia	50	-1.51 (0.17)	18	-0.36 (0.26)	<.001	52	-1.45 (0.16)	21	-0.69 (0.24)	0.01
Vaginal dryness	30	-1.53 (0.21)	19	-1.19 (0.25)	0.29	27	-1.60 (0.23)	15	-1.56 (0.30)	0.91
Vaginal itching	6	-0.87 (0.45)	9	-0.51 (0.41)	0.93	12	-0.86 (0.32)	8	-1.20 (0.48)	0.58
Vaginal burning	7	-0.22 (0.20)	5	-0.64 (0.21)	0.21	7	-0.64 (0.21)	4	-1.39 (0.31)	0.15

Source: Adapted from the Statistical Review from requested information provided on December 13, 2007.
Abbreviations: n = number of subjects satisfying all 3 inclusion criteria; PVC = 0.5 gram (0.3 mg) Premarin® Vaginal Cream; SE = standard error; PVC 21/7 = apply PVC for 21 days and then 7 days off; placebo 21/7 = apply placebo cream for 21 days and then 7 days off; PVC 2x/wk = apply PVC twice a week, continuously; placebo 2X/wk – apply placebo cream twice a week, continuously.
ANCOVA = Analysis of covariance with study site as factor and baseline value as the covariate.

Medical Officer's Comments:

As shown in Table 16, prepared by the Statistical Reviewer, dyspareunia is the only symptom with statistically significant differences between baseline and week 12 for both the PVC 21/7 and PVC 2x/wk treatment groups compared to placebo ($p<0.001$ and $p=0.01$, respectively).

6.1.5 Clinical Microbiology

Per the Chemistry, Manufacturing and Controls review, Study 0713S5-413-NA used drug product manufactured with the approved chemistry, manufacturing and controls. No clinical microbiology consult is needed for sNDA 20-216/SE2-060.

6.1.6 Efficacy Conclusions

The results of the modified MITT population analysis from 12-week, primary, Phase 3b Study 0713S5-413-NA demonstrate the effectiveness of 0.3 mg Premarin® Vaginal Cream (0.5 gram containing 0.625 mg of conjugated estrogens per gram) inserted vaginally twice each week (for example, Monday and Thursday) and 0.3 mg Premarin® Vaginal Cream inserted vaginally daily for 21 days then 7 days off for the treatment of moderate to severe pain associated with sexual activity (dyspareunia) due to menopause ($p=0.01$ for PVC 2x/wk and $p<0.001$ for PVC 21/7). The results also demonstrate that both dosing regimens produced a statistically significant increase in vaginal superficial cells ($p<0.001$, respectively) and a corresponding statistically significant decrease in vaginal parabasal cells ($p<0.001$, respectively) between baseline and week 12 in Study 0713S5-413-NA. A statistically significant reduction in vaginal pH between baseline and week12 compared to placebo was also demonstrated for both treatment regimens ($p<0.001$, respectively).

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In the September 25, 2007 submission of 52-week sNDA 20-216/SE2-060, the 12-week double-blind phase of Study 0713S5-413-NA was complete. The submission reported safety and effectiveness data collected over the initial 12-week, double-blind, placebo-controlled phase of Study 0713S5-413-NA, and preliminary safety data from the open-label safety phase of the study through April 11, 2007, the database snapshot date. The 40-week open-label phase of Study 0713S5-413-NA was ongoing at the time of the September 25, 2007 submission.

The 4-Month Safety Update was submitted on January 25, 2008 and included the final clinical study report for 52-week Study 0713S5-413-NA. Only the final clinical safety findings will be discussed in this review.

Per the submission, primary Phase 3b Study 0713S5-413-NA was undertaken to support the use of Premarin® Vaginal Cream (PVC) for the treatment of postmenopausal vulvar and vaginal atrophy using a twice weekly dosing regimen of PVC (0.3 mg [0.5 g] twice weekly; for example, Monday and Thursday) or the currently approved dosing regimen of daily treatment of PVC 0.3 mg (0.5 g) for 21 days followed by 7 days (b) (4)

Study 0713S5-413-NA was an outpatient, multicenter, double-blind, randomized, placebo controlled (first 12 weeks), Phase 3b clinical trial conducted at 49 sites in Canada and the United States. The first 12 weeks of double-blind, placebo-controlled treatment was followed by a 40-week open-label extension during which subjects assigned to the placebo group in the double-blind phase received PVC but were tabulated in the treatment group to which they were randomly assigned (for example, placebo 21/7 to PVC 21/7). Study 0713S5-413-NA investigated the efficacy and safety of the two low-dose regimens mentioned above. Each dosing regimen was compared with its corresponding placebo group in a 2:1 ratio (active versus placebo).

Safety was evaluated from the results of subject reported signs and symptoms; history reported by the subject; vital signs assessments; scheduled physical examinations; and mammogram, Pap smear, transvaginal ultrasound (TVU) and endometrial biopsies.

Adverse events were recorded throughout Study 0713S5-413-NA and coded using the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) dictionary. Adverse events and treatment-emergent adverse events (TEAE) were summarized by body system and treatment group.

At screening a detailed medical and surgical history was recorded that included any ongoing medical conditions, as well as any acute conditions that resolved within the previous 30 days. A complete physical examination, including a review of systems, was performed and recorded. A twelve-lead electrocardiogram (ECG) was performed. Each subject underwent breast and gynecologic examinations, including a Pap smear (not performed if there was a report of a normal Pap smear within the past 12 months). Microscopic evaluations were performed to test for the presence of vaginal infection (including bacterial vaginosis, *Candida sp., Trichomonas vaginalis, Chlamydia trachomatis,* and *Neisseria gonorrhoeae*). Each subject had to have a mammogram or a report of a normal mammogram performed within the previous 12 months. Transvaginal ultrasound (TVU) was performed to measure double-wall endometrial thickness. An endometrial biopsy was performed at baseline. If the investigator was unable to obtain an endometrial sample at baseline, he/she documented the method(s) used in attempting to obtain a sample. If the central laboratory reported an inadequate sample, it was under the investigator's discretion as to whether or not the subject needed to undergo another endometrial biopsy procedure.

At week 12 and week 52 (or early withdrawal), each subject was to have a physical examination performed, and undergo a breast and gynecologic examination. A Pap smear and mammogram were to be performed if a 12-month period had elapsed since the last one. TVU imaging was performed to measure endometrial double-wall thickness. An endometrial biopsy was also performed at week 52. A biopsy was required at the time of premature withdrawal from the study if at least 12 weeks of treatment had been given, or if the subject experienced abnormal vaginal bleeding at any time during the study. All endometrial samples were sent to a central laboratory for evaluation.

Blood samples for screening laboratory assessments and a urine sample for routine urinalysis and pregnancy test were obtained during screening. Blood samples for laboratory assessments were repeated at visit 6 (week 26) and visit 7 (week 52) or early termination.

Laboratory assessments conducted by a central laboratory included:

Hematology:	hematocrit, hemoglobin, platelet count, red blood cells, white blood cells
Chemistry:	sodium, potassium, chloride, CO2, calcium, phosphorus, glucose (to be assessed when the subject is fasting), blood urea nitrogen, creatinine, total protein, albumin, triglycerides (to be assessed when the subject is fasting), cholesterol (to be assessed when the subject is fasting), uric acid, creatine kinase (CK), total and direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and HbA_{1c} (to be assessed when the subject is fasting)
Urinalysis	pH, protein/albumin, glucose/sugar, leukocytes, nitrites, ketones/acetone, hemoglobin/blood, microscopic analysis
Hormones:	FSH, serum estradiol, and urine pregnancy
Cytology:	Pap (if the Pap smear shows ASCUS, a reflex HPV test will be done), VMI (if the VMI smear shows ASCUS, a reflex HPV test will be done), and endometrial biopsy
STDs:	swab test for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* by DNA probe.

Laboratory assessments conducted at the study site included:

- Specimen prepared with KOH to test for the presence of bacterial vaginosis.
- Specimen prepared with saline to test for the presence of *Candida* sp. and *Trichomonas vaginalis*.
- Blood specimens were collected, in a subset of subjects, at visits 6 and 7 for serum levels of estrone and estradiol.

7.1.1 Deaths

No deaths occurred in primary, Phase 3b Study 0713S5-413-NA.

7.1.2 Other Serious Adverse Events

Per the final study report submitted in the 4-Month Safety Update, a total of 12 subjects had 16 serious adverse events (SAEs) during the conduct of 52-week Study 0713S5-413-NA: "during screening 1 subject had 1 SAE (this subject did not receive test article). During the double-blind phase, 5 subjects each had 1 SAE. During the open-label phase, 6 subjects had 8 SAEs; 2 subjects each had 2 SAEs, and 4 subjects each had 1 SAE. During the follow-up phase, 2 subjects each had 1 SAE."

Per the information provided, Subject (b) (6) had a SAE that occurred during screening (accidental injury [fall resulting in a fractured right ankle]). Subject (b) (6) was subsequently randomized to the placebo 2x/wk treatment group and completed the study. Of the 5 subjects who experienced SAEs during the double-blind phase of Study 0713S5-413-NA, 4 subjects were in the PVC 2x/wk treatment group and 1 subject was in the placebo 2x/wk treatment group (see Table 17).

Per Table 17, adapted by the reviewer from the information provided in the 4-Month Safety Update, a total of 6 subjects experienced 8 SAEs during the open-label phase of Study 0713S5-413-NA. Subject (b) (6), who appeared as a SAE during follow-up in the 4-Month Safety Update, experienced a seizure and was admitted to the hospital in "ventricular fibrillation arrest with cardiogenic shock and symptoms of inferior/posterior myocardial infarction" 2 days after completing Study 0713S5-413-NA. Subjec (b) (6), originally assigned to the placebo 2x.wk treatment group during the double-blind phase, received PVC 2x/wk during the 40-week open-label phase of the study. "This adverse event was assessed by the principle investigator and the medical monitor as serious, life threatening, requiring hospitalization, and definitely unrelated to test article use."

Two subject each experienced 2 SAEs during the open-label phase. Subject (b) (6) (PVC 2x/wk treatment group) experienced shortness of breath, was hospitalized, and subsequently received a "diagnosis of interstitial lung disease due to the autoimmune disorder of scleroderma." Subject (b) (6) (PVC 21/7 treatment group), who presented with a history of diverticulitis during screening, developed a perforation, was hospitalized, and underwent a sigmoid colectomy with splenic flexure mobilization. Approximately 3 months later she experienced a deep vein thrombosis. Both SAEs were considered by the principle investigator and the medical monitor as "definitely not related to use of study medication." See Table 17.

Table 17: Listing of Subjects Reporting Serious Adverse Events by Study Phase, Adverse Event, and Treatment

Body System Adverse Event	PHASE	Treatment	Subject ID
	DOUBLE-BLIND		
Body As a Whole			
Abdominal pain		PVC 2x/wk	(b) (6)
Carcinoma		PVC 2x/wk	(b) (6)

Chest pain		PVC 2x/wk	(b) (6)
Cardiovascular System			
Intracranial aneurysm		Placebo 2x/wk	(b) (6)
Digestive System			
Cholecystitis		PVC 2x/wk	(b) (6)
	OPEN-LABEL		
Body as a Whole			
Scleroderma		PVC 2x/wk	(b) (6)
Cardiovascular System			
Deep vein thrombosis		PVC 21/7	(b) (6)
Myocardial infarct		PVC 2x/wk[a]	(b) (6)
Digestive System			
Gastroenteritis		PVC 21/7	(b) (6)
Gastrointestinal disorder		PVC 21/7	(b) (6)
Cholelithiasis		PVC 2x/wk	(b) (6)
Respiratory System			
Lung disorder		PVC 2x/wk	(b) (6)
Skin and Appendages			
Skin carcinoma		PVC 21/7	(b) (6)

Source: Adapted from sNDA 20-216/SE2-060, 4-Month Safety Update, Table 10-3.
Abbreviations: PVC = Premarin Vaginal Cream; PVC 21/7 = apply PVC daily for 21 days and then 7 days of no therapy (weeks 1 to 52); PVC 2x/wk – apply PVC twice a week, continuously (weeks 1 to 52).
a. During the double-blind phase, this subject was in the placebo 2x/wk group.

Medical Officer's Comments:

As previously stated, Table 17 was adapted by the reviewer from information provided in the 4-Month Safety Update dated January 25, 2008. In total, 11 subjects experienced 13 SAEs during the double-blind and open-label treatment phases of Study 0713S5-413-NA (5 subjects during the double-blind phase and 6 subjects during the open-label phase). These 13 reported SAEs do not raise safety issues for PVC.

7.1.3 Dropouts and Other Significant Adverse Events

Per the 4-Month Safety Update, a total of 26 subjects discontinued during Study 0713S5-413-NA because of adverse events (includes double-blind phase and open-label phase). The following table shows the number and percentage of subjects who withdrew from the study by study phase, treatment group and by the adverse event causing the discontinuation.

Table 18: Number (%) of Subjects Reporting Adverse Events Causing Discontinuation from Study 0713S5-413-NA

STUDY PHASE	Treatment				
Body System Adverse Event	PVC 21/7	Placebo 21/7	PVC 2x/wk	Placebo 2x/wk	Total
DOUBLE-BLIND	n = 143	n = 72	n = 140	n = 68	n = 423
Any Adverse Event	6 (4.2)	1 (1.4)	4 (2.9)	2 (2.9)	13 (3.1)
Body as a Whole					
Abdominal pain	0	0	0	1 (1.5)	1 (0.2)

Carcinoma	0	0	1 (0.7)	0	1 (0.2)
Headache	1 (0.7)	0	0	0	1 (0.2)
Neoplasm	0	0	1 (0.7)	0	1 (0.2)
Pelvic pain	0	1 (1.4)	1 (0.7)	0	2 (0.5)
Digestive System					
Abdominal distention	1 (0.7)	0	0	0	1 (0.2)
Nausea	1 (0.7)	0	0	0	1 (0.2)
Musculoskeletal System					
Arthralgia	0	0	0	1 (1.5)	1 (0.2)
Nervous System					
Dizziness	0	0	1 (0.7)	0	1 (0.2)
Skin and Appendages					
Rash	1 (0.70	0	0	0	1. (0.2)
Urogenital System					
Vaginitis	1 (0.7)	0	0	0	1 (0.2)
Vulvovaginal disorder	1 (0.7)	0	0	0	1 (0.2)
OPEN-LABEL	n = 129	n = 69	n = 132	n = 64	n = 394
Any Adverse Event	2 (1.5)	1 (1.4)	6 (4.5)	4 (6.3)	13 (3.3)
Body as a Whole					
Headache	0	0	1 (0.7)	0	1 (0.2)
Pelvic pain	0	0	1 (0.7)	1 (1.6)	2 (0.5)
Cardiovascular System					
Deep vein thrombosis	1 (0.8)	0	0	0	1 (0.2)
Digestive System					
Gastroesophageal reflux disease	0	0	0	1 (1.6)	1 (0.2)
Metabolic and Nutritional					
Weight gain	0	0	0	1 (1.6)	1 (0.2)
Musculoskeletal System					
Leg cramps	0	1 (1.4)	0	0	1 (0.2)
Nervous System					
Anxiety	0	0	0	1 (1.6)	1 (0.2)
Skin and Appendages					
Alopecia	0	0	1 (0.7)	0	1 (0.2)
Pruritis	0	0	2 (1.5)	0	2 (0.5)
Urogenital System					
Vaginal hemorrhage	0	0	1 (0.7)	0	1 (0.2)
Vulvovaginal disorder	1 (0.8)	0	0	0	1 (0.2)

Source: Adapted from sNDA 20-216/SE2-060, 4-Month Safety Update, Table 10-4.
Abbreviations: PVC = Premarin Vaginal Cream; Double-blind phase: PVC 21/7 = apply PVC daily for 21 days and then 7 days of no therapy; placebo cream 21/7 = apply placebo cream for 21 days and the 7 days of no therapy; PVC 2x/wk = apply PVC twice a week, continuously; placebo cream 2x.wk = apply placebo cream twice a week, continuously: Open-label phase: PVC 21/7 = apply PVC daily for 21 days and then 7 days of no therapy; placebo cream 21/7 = apply PVC daily for 21 days and then 7 days of no therapy; PVC 2x/wk = apply PVC twice a week, continuously; placebo cream 2x.wk = apply PVC cream twice a week, continuously

Medical Officer's Comments:

The total number of adverse events leading to discontinuations during the double-blind phase of Study 0713S5-413-NA was small (3.1%, 13 of 423 treated subjects). The open-label phase also

showed a small number of discontinuation due to adverse events (3.3%, 13 of 394 treated subjects).

The incidence of discontinuations due to adverse events during the double-blind phase were similar between the two active and the two placebo treatment groups (3.5%, 10 of 283 treated subjects in the two PVC treatment groups versus 2.9%, 4 of 140 subjects in the two matching placebo treatment groups). The incidence of discontinuations due to adverse events during the open-label phase, were also similar between the four treatment groups (3.1%, 8 of 261 subjects in the two original PVC treatment groups versus 3.7%, 4 of 133 subjects in the two original matching placebo treatment groups who received PVC during the open-label phase).

The reported discontinuations due to adverse events during 52-week Study 0713S5-413-NA do not raise safety issues.

7.1.3.1 Overall profile of dropouts

Of the 423 subjects in the safety population, 306 subjects (72.3%, 306 of 423 treated subjects) experienced adverse events (AEs) in the 12-week double-blind phase of Study 0713 S5-413-NA.

All 423 subjects in the safety population were followed up after their last visit, whether they discontinued participation in the study or completed the study. During the follow-up period, 180 subjects (42.6%) in the safety population had at least 1 AE. The AEs were considered to be mild for 94 subjects (23.8%), moderate for 162 (41.1%), and severe for 1 subject (0.2%) who was randomized to placebo 2x/wk during the double-blind phase and PVC 2x/wk during the open-label phase.

TEAEs were reported for 288 of the 423 subjects in the safety population (68.1%) during the double-blind phase of the study and for 277 of the 394 subjects (70.3%) who entered the open-label phase of the study.

A total of 13 subjects (3.1%) discontinued their participation in the study because of an adverse event during the double-blind phase of Study 0713S5-413.NA. A total of 13 subjects (3.3%) discontinued their participation in the study because of an adverse event during the open-label phase of the study. See Table 18.

7.1.3.2 Adverse events associated with dropouts

Adverse events leading to discontinuation during the double-blind and open-label phases in Study 0713S5-413-NA included:

<u>Double-blind:</u>

Headache, pelvic pain, abdominal pain/distention, nausea, anxiety, dizziness, arthralgia, vaginitis/vulvovaginal disorder, and rash.

Open-label:

Headache, pelvic pain, vaginal hemorrhage, deep vein thrombosis, weight gain, leg cramps, anxiety, vulvovaginal disorder, gastroesophageal reflux disease, pruritis and hair loss.

Medical Officer's Comments:

The adverse events reported during the conduct of Study 0713S5-413-NA are known to occur with the use of estrogen therapy and do not raise safety issues.

7.1.3.3 Other significant adverse events

Endometrial Thickness:

All subjects were required to undergo a transvaginal ultrasound (TVU) at screening and at week 52 (or sooner if clinically indicated and at early termination). Subjects whose endometrial thickness measurements by TVU were ≥ 5 mm at screening were not eligible for enrollment.

One subject in the PVC 21/7 treatment group discontinued after 42 days of participation with exacerbation of vaginal burning (Subject (b) (6)). Her TVU was 5.2 mm and her endometrial biopsy was reported as normal.

Thirty (30) subjects (7.1%, 30 of 423 subjects in the MITT population) had an endometrial thickness, measured by TVU, ≥ 5 mm at week 52 or at early termination. The following presentation demonstrates the information available for these 30 subjects:

Subjects treated with PVC 21/7 for the full 52 weeks (or until early termination) of Study 0713S5-413-NA:

Subject ID	Baseline	End of study	Endometrial Biopsy Report	Follow-up
(b) (6)	4.7 mm	8.3 mm (day 371)	Not obtained; atrophy	D&C: atrophic endometrium
(b) (6)	3.0 mm	10.0 mm (day 371)	Insufficient tissue for evaluation	Repeat biopsy; inactive endometrium
(b) (6)	4.0 mm	5.2 mm (day 45)	No evidence of hyperplasia or malignancy	No follow-up recommended
(b) (6)	2.4 mm	6.1 mm (day 366)	Not obtained; cervical stenosis	D&C: no endometrium identified
(b) (6)	1.7 mm	6.7 mm	Benign surface	No follow-up

		(day 346)	endometrial tissue	recommended
(b) (6)	1.8 mm	9.0 mm (day 364)	Insufficient tissue for evaluation	Hysteroscopy: atrophic endometrium and polyp
(b) (6)	1.9 mm	9.0 mm (day 359)	Not obtained; cervical stenosis	D&C: benign endometrium
(b) (6)	2.2 mm	5.0 mm (day 352)	Not obtained; cervical stenosis	Repeat TVU recommended
(b) (6)	4.7 mm	5.5 mm (day 365)	Insufficient tissue for evaluation; scant amt. benign endometrium	No follow-up recommended
(b) (6)	3.5 mm	7.0 mm (day 372)	Insufficient tissue for evaluation	Sono-hysterogram: no polyp; repeat TVU normal
(b) (6)	N/A	N/A	Bleeding at Week 26; Biopsy: proliferative endometrium	
(b) (6)	3.0 mm	5.0 mm (day 366)	Week 52: Insufficient tissue for evaluation	D&C: atrophic endometrium
(b) (6)	4.8 mm	5.0 mm (day 371)	Insufficient tissue for evaluation; scant amt. benign endometrium	No follow-up recommended
(b) (6)	1.6 mm	9.0 mm (day 367)	Insufficient tissue for evaluation	Hysteroscopy: polyp; D&C: proliferative endometrium

Subjects treated with PVC 2x/wk for the full 52 weeks of Study 0713S5-413-NA:

(b) (6)	2.5 mm	7.4 mm (day 372)	Insufficient tissue for evaluation	D&C: benign endometrial tissue with polyp
(b) (6)	3.4 mm	5.0 mm (day 367)	Insufficient tissue for evaluation; scant amt. benign endometrium	No follow-up recommended
(b) (6)	3.0 mm	9.9 mm (day 366)	No endometrial tissue identified	Repeat TVU 3.7 mm
(b) (6)	3.0 mm	5.9 mm (day 360)	No endometrial tissue identified	Repeat TVU: 3.0 mm
(b) (6)	4.7 mm	8.0 mm (day 370)	Benign endometrial tissue	No follow-up recommended

(b) (6)	4.5 mm	5.0 mm (day 378)	Insufficient tissue for evaluation	No follow-up recommended
(b) (6)	3.4 mm	7.0 mm (day 358)	Proliferative endometrium: benign	No follow-up recommended

Subjects initially treated with placebo 21/7 for the first 12-weeks of Study 0713S5-413-NA then treated with PVC 21/7 for the remaining 40-week open-label phase:

(b) (6)	4.5 mm	5.0 mm (day 371)	Insufficient tissue for evaluation; scant amt. benign endometrium	No follow-up recommended
(b) (6)	2.0 mm	5.0/6.0 mm (day 357)/ (day 603)	Insufficient tissue for evaluation	Repeat TVU: 6.0 mm; TVU on 05 Jul 07; 6.0 mm
(b) (6)	2.0 mm	6.0/6.0 mm (day 373)/ (day 548)	Benign atrophic endometrium	Repeat TVU: 6.0 mm
(b) (6)	4.0 mm	8.0 mm (day 390)	No tissue identified	Follow-up requested; pending
(b) (6)	4.0 mm	7.0 mm (day 366)	Insufficient tissue for evaluation	Follow-up requested; pending

Subjects initially treated with placebo 2x/wk for the first 12-weeks of Study 0713S5-413-NA then treated with PVC 2x/wk for the remaining 40-week open-label phase:

(b) (6)	3.0 mm	5.2/7.9 mm (day 372)/ (day 503)	Insufficient tissue for evaluation	D&C hysteroscopy; scant benign endometrium
(b) (6)	4.0 mm	5.0 mm (day 377)	Insufficient tissue for evaluation; scant amt. benign endometrium	No follow-up recommended
(b) (6)	1.6 mm	9.7 mm (day 372)	3 unsuccessful attempts; cervical stenosis	D&C/ hysteroscopy; benign endometrium
(b) (6)	4.1 mm	5.3 mm (day 367)	Insufficient tissue for evaluation; scant amt. benign endometrium	No follow-up recommended
(b) (6)	4.5 mm	8.0 mm (day 369)	Insufficient tissue for evaluation	Follow-up requested;

pending

Medical Officer's Comments:

From the reported findings, twice as many subjects in the PVC 21/7 treatment group experienced endometrial thickness ≥ 5 mm (13 subjects) than in the PVC 2x/wk treatment group (7 subjects) after 52 weeks of use. However, no difference was noted between the two PVC treatment regimens over 40 weeks of open-label use (5 subjects each per treatment regimen). Two subjects with TVU results ≥ 5 mm were reported to have proliferative endometrium at week 52 (Subject (b) (6) in the PVC 21/7 treatment group and Subject (b) (6) in the PVC 2x/wk treatment group).

Only one of the 30 subjects listed above was evaluated for vaginal bleeding (Subject (b) (6) in the PVC 21/7 treatment group; week 26). This subject was reported to have a proliferative endometrium at week 26 and endometrial atrophy at week 52.

Overall, adequate follow-up was observed in Study 0713S5-413-NA for subjects with endometrial thickness ≥ 5 mm. Follow-up procedures performed when no or insufficient endometrial tissue was obtained on endometrial biopsy included: repeat endometrial biopsy, repeat TVU, hysteroscopy, sonohysterogram, or dilatation and curettage (D&C). However, 4 subjects who were recommended to have follow-up procedures performed did not:

- *Subject (b) (6) received PVC 21/7 for 52 weeks; no endometrial biopsy obtained due to cervical stenosis at week 52; TVU on day 352 was reported as 5.0 mm (baseline reported as 2.2 mm); a repeat TVU was recommended*
- *Subject (b) (6) received PVC 21/7 for 40 weeks during the open-label phase of Study 0713S5-413-NA; insufficient endometrial tissue for evaluation on endometrial biopsy; TVU on day 390 was reported as 8.0 mm (baseline reported as 4.0 mm); subject refused to have repeat TVU*
- *Subject (b) (6) received PVC 21/7 for 40 weeks during the open label phase of Study 0713S5-413-NA; insufficient endometrial tissue for evaluation on endometrial biopsy; TVU on day 366 was reported as 7.0 mm (baseline reported as 4.0 mm); subject refused to have repeat TVU*
- *Subject (b) (6) received PVC 2x/wk for 40 weeks during the open label phase of Study 0713S5-413-NA; insufficient endometrial tissue for evaluation on endometrial biopsy; TVU on day 369 was reported as 8.0 mm (baseline reported as 4.5 mm); subject refused to have repeat TVU*

The outcome for these 4 subjects is unknown.

Endometrial biopsy:

Endometrial biopsies were required for all randomly assigned subjects at week 52 (or sooner if clinically indicated or at early termination). In the submission, a total of 215 subjects with a uterus were treated with 0.3 mg (0.5 g) PVC 21/7 (143 subjects randomized to PVC 21/7 at

baseline and 72 subjects switched from placebo 21/7 to PVC 21/7 at week 13). A total of 208 subjects with a uterus were treated with 0.3 mg (0.5 g) PVC 2x/wk (140 subjects randomized to PVC 2x/wk at baseline and 68 subjects switched from placebo 2x/wk to PVC 2x/wk at week 13).

Per the 4-Month Safety Update, 166 subjects across the 4 treatment groups in Phase 3b Study 0713S5-413-NA (39.2%, 166 of 423 treated subjects) did not have endometrial biopsy results reported. The endometrial biopsy reports for the 423 subjects in the MITT population are summarized as follows. The PVC 21/ 7 regimen includes subjects switched from placebo 21/7 during the double-blind phase to PVC 21/7 during the open-label phase. The PVC 2x/wk regimen includes subjects switched from placebo 2x/wk during the double-blind phase to PVC 2x/wk during the open-label phase.

Endometrial Biopsy Results	PVC 21/7 Regimen	PVC 2x/wk Regimen
Scant endometrial tissue, no hyperplasia or cancer	55	44
No endometrial tissue identified	39	63
Normal	24	22
Proliferative	6	6
Not done	92	74

For subjects whose endometrial biopsies were reported as “not done”, the reasons included the following:

Endometrial Biopsy “Not Done”	PVC 21/7 Regimen	PVC 2x/wk Regimen
Subject refusal	27	25
Cervical stenosis	30	25
Subject withdrew consent	11	2
Early termination due to adverse event	5	8
Early termination due to protocol violation	1	2
Subject lost to follow-up	12	9
Discontinued by investigator	0	1
Clinical site omission	1	0

Endometrial atrophy	4	1
Endometrial biopsy attempted, no tissue	1	1

Medical Officer's Comments:

Per the information provided, 42.8% of subjects treated with PVC 21/7 (a total of 92 subjects) and 35.6% of subjects treated with PVC 2x/wk (a total of 74 subjects) did not have endometrial biopsy results reported. Refusal to have an endometrial biopsy performed and cervical stenosis accounted for the majority of these subjects who did not have an endometrial biopsy performed at end-of-study or early termination (12.3% refused, 52 of 423 MITT population; 13% had cervical stenosis, 55 of 423 MITT population). Other 52-week clinical trials have reported similar reasons for not obtaining an endometrial biopsy at end-of-study or at early termination.

In Study 0713S5-413-NA, no cases of endometrial hyperplasia or endometrial carcinoma were reported for the 155 subjects who had evaluable endometrial biopsies (83 subjects who received PVC 21/7 during the double-blind phase and/or the open-label phase, and 72 subjects who received PVC 2x/wk during the double-blind phase and/or the open-label phase).

Twelve (12) subjects with endometrial biopsy results at end-of-study were reported to have proliferative endometrium (6 cases of proliferative endometrium in the PVC 21/7 treatment groups and 6 cases in the PVC 2x/wk treatment groups):

Subject ID	Treatment	Baseline TVU/ endometrial biopsy	End-of Study TVU/ endometrial Biopsy
(b) (6)	PVC 21/7	1.5 mm/tissue insufficient for diagnosis	2.7 mm/weakly proliferative endometrium (day 368)
(b) (6)	PVC 21/7	Not measurable	2.3 mm/disaggregated proliferative endometrium (day 373)
(b) (6)	PVC 21/7	1.2 mm/tissue insufficient for diagnosis	0.6 mm/disaggregated surface endometrium and proliferative glands (day 371)
(b) (6)	PVC 21/7	1.5 mm/ endometrial atrophy; tissue insufficient tissue for diagnosis	4.5 mm/disaggregated proliferative endometrium (day 368)
(b) (6)	PVC 21/7	1.6 mm/endometrial atrophy; tissue insufficient for diagnosis	9.0 mm/scant endometrial tissue; insufficient for diagnosis (day 367)
(b) (6)	PVC 21/7	1.9 mm/inactive endometrium; suggest atrophy	2.6 mm/scant fragments of dyssynchronous endometrium; detached proliferative and secretory-type glands (day 372)

(b) (6)	PVC 2x/wk	1.4 mm/ scant endometrial tissue; suggest atrophy	4.4 mm/polypoid fragment with proliferative glands; no atypia; benign endometrial polyp (day 360)
(b) (6)	PVC 2x/wk	2.8 mm/ scant endometrial tissue insufficient for diagnosis	4.8 mm/ proliferative endometrium (day 315)
(b) (6)	PVC 2x/wk	2.7 mm/scant endometrial tissue insufficient for diagnosis	2.9 mm/weakly proliferative endometrium (day 379)
(b) (6)	PVC2x/wk	2.0 mm/scant atrophic endometrium	4.0 mm/disaggregated weakly proliferative endometrium (day 345)
(b) (6)	PVC 2x/wk	3.4 mm/scant endometrial tissue insufficient for diagnosis	7.0 mm/proliferative endometrium (day 358)
(b) (6)	PVC 2x/wk	4.0 mm/superficial endometrial tissue; suggest atrophy	3.0 mm/proliferative endometrium (day 404)

* Subject (b) (6) received placebo 21/7 during the 12-week double-blind phase of Study 0713S5-413-NA and PVC 21/7 during the 40-week open-label phase.

Medical Officer's Comments:

Two additional subjects were diagnosed with proliferative endometrium during the conduct of Study 0713S5-413-NA. Subject (b) (6)*, in the PVC 21/7 treatment group, was diagnosed with proliferative endometrium on day 284. She completed the study and on Day 366 her endometrial biopsy was reported as follows: "Sections demonstrate a scant amount of endometrium. The specimen consists of few thin strips of superficial endometrial lining and minimal stroma. There is no evidence of hyperplasia or malignancy." Subject* (b) (6)*, in the PVC 2x/wk treatment group, was evaluated for vaginal bleeding on day 223 (resolved spontaneously) and again on day 258. At her early termination visit, a D & C was performed in lieu of an endometrial biopsy due to continued vaginal bleeding. The D & C results were reported as: "Benign fragments of proliferative endometrium with no evidence of hyperplasia or malignancy."*

The occurrence of proliferative endometrium is not unexpected when a woman with a uterus is treated with unopposed estrogen. It is important, however, that labeling advise patients and healthcare providers of the need for close clinical surveillance, including adequate diagnostic measure in all cases of unusual vaginal bleeding. The addition of a progestin is generally recommended for women with a uterus to reduce the chance of getting cancer of the uterus.

7.1.4 Other Search Strategies

No algorithm involving combination of clinical findings and a marker for a particular toxicity was developed with the exception of the interrelationship on endometrial hyperplasia and unopposed estrogen use discussed in Subsection 7.1.3.3, "Other significant adverse events".

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Per the submission, safety is summarized for all subjects who applied at least 1 dose of study medication. Safety was evaluated from the results of subject reported signs and symptoms, history reported by the subject, vital sign assessments, scheduled physical examinations, and diagnostic assessment performed (mammogram, Pap smear, TVU, and endometrial biopsy).

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Per the submission, all reported adverse events were coded using the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) dictionary. Adverse events and treatment-emergent adverse events (TEAE) were summarized by body system and treatment group.

7.1.5.3 Incidence of common adverse events

In Study 0713S5-413-NA, all adverse events occurring during the double-blind and open-label phases were considered treatment-emergent. Treatment-emergent adverse events were experienced by between 63.9% and 71.4% of all randomized subjects across the 4 treatment groups during the double-blind phase and between 68.1% and 76.6% of randomized subjects during the open-label phase. There was a higher incidence of overall treatment-emergent events in the body as a whole class (includes abdominal pain, accidental injury, back pain, headache, infection, and pain) in both phases of Study 0713S5-413-NA. See Table 19.

7.1.5.4 Common adverse event tables

Table 19: Number (%) of Subjects Reporting Treatment-Emergent Adverse Events ≥ 5% in Any Treatment Group, by Study Phase and Treatment

STUDY PHASE	**Treatment**				
Body System Adverse event	PVC 21/7	Placebo 21/7	PVC 2x/wk	Placebo 2x/wk	Total
DOUBLE-BLIND	n = 143	n = 72	n = 140	n = 68	n = 423
Any adverse event	95 (66.4)	46 (63.9)	100 (71.4)	47 (69.1)	288 (68.1)
Body as a Whole					

Abdominal pain	11 (7.7)	2 (2.8)	9 (6.4)	6 (8.8)	28 (6.6)
Accidental injury	5 (3.5)	5 (6.9)	9 (6.4)	3 (4.4)	22 (5.2)
Back pain	7 (4.0)	3 (4.2)	13 (9.3)	5 (7.4)	28 (6.6)
Headache	14 (9.8)	8 (11.1)	26 (18.6)	12 (17.6)	60 (14.2)
Infection	7 (4.9)	5 (6.9)	16 (11.4)	5 (7.4)	33 (7.8)
Pain	10 (7.0)	3 (4.2)	4 (2.9)	4 (5.9)	21 (5.0)
Cardiovascular System					
Vasodilatation	5 (3.5)	4 (5.6)	7 (5.0)	1 (1.5)	17 (4.0)
Digestive System					
Diarrhea	4 (2.8)	2 (2.8)	10 (7.1)	1 (1.5)	17 (4.0)
Nausea	5 (3.5)	4 (5.6)	3 (2.1)	4 (5.9)	16 (3.8)
Musculoskeletal System					
Arthralgia	4 (2.8)	5 (6.9)	5 (3.6)	4 (5.9)	18 (4.3)
Nervous system					
Insomnia	5 (3.5)	3 (4.2)	4 (2.9)	4 (5.9)	16 (3.8)
Urogenital System					
Breast pain	8 (5.6)	2 (2.8)	4 (2.9)	0 (0)	14.0 (3.3)
Leukorrhea	3 (2.1)	2 (2.8)	4 (2.9)	6 (8.8)	15 (3.5)
Urinary frequency	4 (2.8)	3 (4.2)	8 (5.7)	3 (4.4)	18 (4.3)
Urinary urgency	3 (2.1)	3 (4.2)	6 (4.3)	4 (5.9)	16 (3.8)
Vaginitis	8 (5.6)	3 (4.2)	7 (5.0)	3 (4.4)	21 (5.0)
OPEN-LABEL	n = 129	n = 69	n = 132	n = 64	n = 394
Any adverse event	89 (69.0)	47 (68.1)	92 (69.7)	49 (76.6)	277 (70.3)
Body as a Whole					
Abdominal pain	3 (2.3)	4 (5.8)	6 (4.5)	4 (6.3)	17 (4.3)
Accidental injury	11 (8.5)	6 (8.7)	13 (9.8)	5 (7.8)	35 (8.9)
Back pain	4 (3.1)	2 (2.9)	10 (7.6)	6 (9.4)	22 (5.6)
Flu syndrome	1 (1.6)	3 (4.3)	6 (4.5)	5 (7.8)	16 (4.1)
Headache	11 (8.5)	5 (7.2)	19 (14.4)	12 (18.8)	47 (11.9)
Infection	12 (9.3)	5 (7.2)	11 (8.3)	4 (6.3)	32 (8.1)
Pain	10 (7.8)	4 (5.8)	6 (4.5)	5 (7.8)	25 (6.3)
Digestive system					
Gastroesophageal reflux disease	1 (0.8)	0 (0)	2 (1.5)	4 (6.3)	7 (1.8)
Musculoskeletal System					
Arthralgia	8 (6.2)	4 (5.8)	12 (9.1)	7 (10.9)	31 (7.9)
Nervous System					
Insomnia	4 (3.1)	0 (0)	4 (3.0)	4 (6.3)	12 (3.0)
Respiratory System					
Cough increased	2 (1.6)	0 (0)	7 (5.3)	5 (7.8)	14 (3.6)
Pharyngitis	3 (2.3)	2 (2.9)	8 (6.1)	2 (3.1)	15 (3.8)
Sinusitis	7 (5.4)	2 (2.9)	3 (2.3)	3 (4.7)	15 (3.8)
Upper respiratory infection	0 (0)	0 (0)	3 (2.3)	5 (7.8)	8 (2.0)
Urogenital System					
Dysuria	4 (3.1)	4 (5.8)	3 (2.3)	1 (1.6)	12 (3.0)
Urinary frequency	3 (2.3)	5 (7.2)	4 (3.0)	1 (1.6)	13 (3.3)
Vaginitis	8 (6.2)	10 (14.5)	8 (6.1)	4 (6.3)	30 (7.6)

Source: Adapted from sNDA 20-216/SE2-060 4-Month Safety Update, Final Report, Table10-1, page 75.
Abbreviations: PVC = Premarin Vaginal Cream; PVC 21/7 – apply PVC for 21 days and then 7 days of no therapy (full 52 weeks); placebo 21/7 = apply placebo cream for 21 days and then 7 days with no therapy for 12 weeks (double-blind) then apply PVC 21/7 for 40 weeks (open-label); PVC 2x/wk = apply PVC twice a week continuously

(full 52 weeks); placebo 2x/wk = apply placebo cream twice a week for 12 weeks (double-blind) then apply PVC 2x/wk for 40 weeks (open-label).

Medical Officer's Comments:

As shown in Table 19, the most common adverse events across the 4 treatment groups in both the double-blind and open-label phases of Study 0713 S5-413-NA were in the body as a whole system. Vaginitis, under the urogenital system, was also commonly reported during the open-label phase.

The common adverse events reported in Study 0713S5-413-NA are not unknown with estrogen alone therapy and have been reported to occur in other clinical trials of hormone therapy conducted for a VVA indication.

7.1.5.5 Identifying common and drug-related adverse events

TEAEs reported by ≥ 5% of the subjects in any treatment group during the double-blind phase (weeks 1 through 12) of Study 0713S5-413-NA are summarized by treatment group in Table 18. As shown, a higher incidence of nausea, arthralgia, and insomnia were reported in the combined placebo treatment groups compared with the combined PVC treatment groups. However, a higher incidence of breast pain and vaginitis was reported in the combined PVC treatment groups as compared with the combined placebo treatment groups.

In the 12-week double-blind portion of Study 0713S5-413-NA, the incidence of breast pain reported in the PVC 21/7 treatment group was approximately twice that reported in the PVC 2x/wk treatment group. However, the incidence of headache in the PVC 2x/wk treatment group was approximately twice that reported in the PVC 21/7 treatment group.

Medical officer's Comments:

The common adverse events reported during the double-blind phase of Study 0713S5-413-NA are not unknown with estrogen alone therapy. Similar incidences of adverse events were reported across the 4 treatment groups with those exceptions previously noted.

7.1.5.6 Additional analyses and explorations

No additional analyses were performed on the reported most common treatment-emergent adverse events.

7.1.6 Less Common Adverse Events

See the discussion regarding Premarin® Vaginal Cream use and reported endometrial findings in Sub-section 7.1.3.3 "Other significant adverse events".

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Per the protocol submitted for Phase 3b Study 0713S5-413-NA under IND 72,606, clinical laboratory tests were conducted at screening to determine eligibility. In addition, serum estradiol and estrone levels were obtained at week 52 in a limited number of subjects.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Per the protocol submitted for Phase 3b Study 0713S5-413-NA under IND 72,606, clinical laboratory tests were conducted at screening to determine eligibility. In addition, serum estradiol and estrone levels were obtained at week 52 in a limited number of subjects.

7.1.7.3 Standard analyses and explorations of laboratory data

Per the protocol submitted for Phase 3b Study 0713S5-413-NA under IND 72,606, clinical laboratory tests were conducted at screening to determine eligibility. In addition, serum estradiol and estrone levels were obtained at week 52 in a limited number of subjects.

7.1.7.3.1 Analyses focused on measures of central tendency

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

7.1.7.4 Additional analyses and explorations

Per the protocol submitted for Phase 3b Study 0713S5-413-NA under IND 72,606, clinical laboratory tests were conducted only at screening to determine eligibility. In addition, serum estradiol and estrone levels were obtained at week 52 in a limited number of subjects.

7.1.7.5 Special assessments

A bioavailability study, Study 0713S5-414-US titled, "A Multiple-Dose, Comparative Bioavailability Study of Premarin Vaginal Cream Versus Premarin Oral Tablets in Postmenopausal Women with Atrophic Vaginitis" was conducted to characterize the systemic exposure and bioavailability at steady state of 0.5 g (0.3 mg) of Premarin® Vaginal Cream (PVC) and 0.3 mg Premarin® oral tablet in postmenopausal women with atrophic vaginitis. This was an open-label, randomized, multiple-dose, 2-treatment, 2-period crossover study conducted in generally healthy postmenopausal women, aged 45 to 80 years (mean age 57.5 years), with atrophic vaginitis. Twenty-four (24) subjects were enrolled and completed, and PK data were obtained for all subjects for both PVC and Premarin® tablet formulations.

Premarin® Vaginal Cream (0.5 g [0.3 mg]) and 0.3 mg Premarin® oral tablets were each administered for 7 days: days 1 to 7 (period 1) and days 8 to 14 (period 2). Subjects were randomly assigned to receive either PVC or tablet during the first period. There was no washout period between treatment periods. Both study medications were administered in the morning at approximately the same time each day. The inclusion/exclusion criteria were the same as in primary, Phase 3b Study 0713S5-413-NA.

Blood samples for baseline hormones were collected on day -2, day -1, and day 1 before the first administration of study medication. Serial blood samples for PK analysis were collected on days 7 and 8 of each treatment period at the following times: immediately before dosing for baseline determination) and at 1.5, 3, 4.5, 6, 7.5, 9, 10.5, 12, 16, and 24 hours after dose administration. The PK analysis of plasma concentrations was performed by the Clinical Pharmacokinetics group of Wyeth Research for the following components of Premarin: unconjugated and total (unconjugated plus conjugated) estrone, equilin, and 17β-estradiol. Plasma concentrations for estrone and estradiol were analyzed with and without adjustment for baseline concentrations since both hormones are endogenous in women.

Values for C_{max}, the time to reach C_{max} (t_{max}), and minimum concentration (C_{min}) were calculated. The steady state area under the concentration-time curve (AUC_{ss}) was calculated from zero to τ was the dose interval of 24 hours. Average concentration (C_{avg}) was calculated by AUC_{ss}/τ. Relative bioavailability (F) was calculated as:

$$F = \frac{AUC_{ss} \text{ following vaginal administration}}{AUC_{ss} \text{ following oral administration.}}$$

Per the final study report (CSR-63983), the mean unconjugated estradiol steady state C_{max} (uncorrected for baseline) after daily vaginal administration (7 days) of 0.5 g (0.3 mg) of Premarin® Vaginal Cream was 12.8 ± 16.6 pg/mL versus 19.4 ± 24.7 pg/mL for 0.3 mg Premarin® Tablets. The mean unconjugated estrone steady state C_{max} (uncorrected for baseline) after daily vaginal administration (7 days) of 0.5 g (0.3 mg) of Premarin® Vaginal Cream was 42.0 ± 13.9 pg/mL versus 70.2 ± 32.6 pg/mL for 0.3 mg Premarin® Tablets. Study 0713S5-414-US demonstrates that systemic exposure to estradiol and estrone was lower with Premarin®

Vaginal Cream than with Premarin® Tablets (mean relative bioavailability was 81% for unconjugated estradiol and 71% for unconjugated estrone).

Medical Officer's Comments:

(b) (4)

In this submission, the Clinical Pharmacology Reviewer recommends that the pharmacokinetic finding for PVC in Study 0713S5-414-US be included in labeling to demonstrate the systemic exposure of Premarin® Vaginal Cream.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs (blood pressure and pulse) were obtained at screening and at each scheduled visit (visit 2 [day 1], visit 3 [day 28], visit 4 [day 42], visit 5 [day 84], visit 6 [day 182], and visit 7 [day 365]). Baseline values were defined as the last observation prior to the first dose of study medication. Potentially clinical significant values were identified for sitting systolic/diastolic blood pressure and pulse. The criteria used were:

- Sitting systolic blood pressure: ≥ 180 mm Hg or an increase of ≥ 20 mm Hg compared to baseline or ≤ 90 mm Hg of a decrease of ≥ 20 mm Hg compared to baseline
- Sitting diastolic blood pressure: ≥ 105 mm Hg or an increase of ≥ 15 mm Hg compared to baseline or ≤ 50 mm Hg of a decrease of ≥ 15 mm Hg compared to baseline
- Pulse: ≤ 50 beats per minute or ≥ 100 beats per minute.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

In this submission, the safety population included all randomized subjects who received at least 1 dose of study medication. During the 12-week double-blind phase of Study 0713S5-413-NA, there were 423 subjects included in the safety population (143 subjects in the PVC 21/7 treatment group, 72 subjects in the placebo 21/7 treatment group, 140 subjects in the PVC 2x/wk treatment group, and 68 subjects in the placebo 2x/wk treatment group). During the 40-week open-label phase of Study 0713S5-413-NA, there were 394 subjects in the safety population (129 subjects in the PVC 21/7 treatment group, 69 subjects in the placebo 21/7 treatment group who received PVC 21/7, 132 subjects in the PVC 2x/wk treatment group, and 64 subjects in the placebo 2x/wk treatment who received PVC 2x/wk).

7.1.8.3 Standard analyses and explorations of vital signs data

Per the submission, there were no clinically important findings for the assessments of blood pressure and pulse during the conduct of Study 0713S5-413-NA. No additional analysis of vital signs data was performed by this reviewer.

7.1.8.3.1 Analyses focused on measures of central tendencies

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.8.3.3 *Marked outliers and dropouts for vital sign abnormalities*

7.1.8.4 Additional analyses and explorations

No additional analyses of vital signs data was performed by this reviewer.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Electrocardiograms were only obtained at baseline in primary Phase 3b Study 0713S5-413-NA.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

No overall drug-control comparisons were made.

7.1.9.3 Standard analyses and explorations of ECG data

No standard analyses and exploration of ECG data were performed/conducted.

7.1.9.3.1 Analyses focused on measures of central tendency

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

7.1.9.4 Additional analyses and explorations

No QT or QT_c interval data is included in the submission. One case of "ventricular fibrillation arrest with cardiogenic shock and symptoms of inferior/posterior myocardial infarction" in a subjects who received placebo 2x/wk for the first 12 weeks of Study 0713S5-413-NA and Premarin® Vaginal Cream 2x/week during the 40-week open label phase of the study. No cases of Torsades de pointes or ventricular tachycardia were reported in the safety data.

7.1.10 Immunogenicity

No human immunogenicity studies, data, or published literature were submitted with the sNDA.

7.1.11 Human Carcinogenicity

No human carcinogenicity studies were conducted under IND 72,606 for Premarin® Vaginal Cream. No data or published literature was submitted with the sNDA on human carcinogenicity.

Currently, the Agency recommends that the following information be included in estrogen class labeling: "Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testes, and liver."

7.1.12 Special Safety Studies

No special safety studies were conducted during the drug development program for Premarin® Vaginal Cream.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Per the submission, there were no cases of overdose with the study medication in the clinical development program of Premarin® Vaginal Cream.

7.1.14 Human Reproduction and Pregnancy Data

Given that the indication being sought in sNDA 20-216/SE2-060 is the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, no formal studies in humans on the effects of Premarin® Vaginal Cream in human reproduction or pregnancy were performed.

Primary Phase 3b Study 0713S5-413-NA did not provide any information on drug exposure in pregnant women.

7.1.15 Assessment of Effect on Growth

Premarin® Vaginal Cream has not been tested in pediatric subjects.

Premarin® oral therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay. Safety and effectiveness of Premarin® oral therapy in pediatric patients have not otherwise been established.

"Large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, which could result in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. If estrogen is administered to patients whose bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended during estrogen administration."

"Estrogen treatment of prepubertal girls also induces uterine bleeding. In boys, estrogen treatment may modify the normal pubertal process and induce gynecomastia."

7.1.16 Overdose Experience

No cases of overdose with Premarin® Vaginal Cream have been reported during the drug development program.

7.1.17 Postmarketing Experience

Premarin® Cream was marketed in 1946 under NDA 05-900 for vaginal use for atrophic vaginitis and for use for acne vulgaris. In 1949, Premarin® Vaginal Cream was developed and labeled in "the treatment of atrophic vaginitis and kraurosis vulvae". ANDA 83-273 for Premarin® Vaginal Cream (0.625 mg conjugated estrogens per gram of cream) was approved by the Agency on October 16, 1978.

The Division of Drug Risk Evaluation (DDRE) was consulted for a safety review for Premarin® Vaginal Cream. Per the consultation, the term "data mining" refers to the use of computerized algorithms to discover hidden patterns of associations or unexpected occurrences (i.e., "signals") in large databases. These signals can then be evaluated for intervention as appropriate. The WebVDME data mining application from Lincoln Technologies was searched on 1/14/08 using the trade name Premarin®. In addition, the Adverse Event Reporting System (AERS) was searched as follows:

- Any report with the suspect drug Premarin® Vaginal Cream listed as the Trade Name.

- Any report with the suspect drug Premarin® listed as the Trade Name with the following routes of administration noted: vaginal, topical, cutaneous, endocervical.

"Due to the volume of reports for this medication, no attempt was made to eliminate duplicates or reports received inadvertently."

Per the completed searches, the "highest data mining scores and the most commonly reported preferred terms were related to breast cancer. Other preferred terms with high data mining scores relate to endometrial cancer, ovarian cancer and thromboembolic events."

A search of the AERS database for any report with the suspect drug Premarin® Vaginal Cream listed as the Trade name retrieved 49 cases. The most commonly reported preferred terms were vaginal infection, breast pain, pruritis, abdominal pain, alopecia, breast cancer female, dermatitis, drug ineffective, pain, vaginal discharge, hyperhidrosis, nausea, pruritis genital, urinary tract infection, vaginal candidiasis, vaginal hemorrhage, and vaginal pain. Per the consult, there "were too few reports retrieved using this search strategy to draw any further conclusions."

A search of the AERS database for any report with the suspect drug Premarin® and the queried route of administration (vaginal, topical, cutaneous, endocervical) retrieved 926 cases. The most commonly reported preferred terms were: vaginal infection, application site reaction, pain, drug ineffective, breast pain, pruritis, abdominal pain, dermatitis, headache, breast cancer, alopecia, condition aggravated, dizziness, hypersensitivity, nausea, vaginal candidiasis, depression vaginal hemorrhage, vaginal discharge, breast enlargement, cystitis, menometrorrhagia, vulvovaginitis, etc. This search "did not identify any new or unexpected adverse events terms for consideration as additions to the proposed labeling."

Medical Officer's Comments:

The DDRE consult confirmed that data mining scores and searches of the AERS database for Premarin® Vaginal Cream did not identify any unlabeled adverse event terms for consideration as additions to the proposed labeling.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The table of clinical studies that appears in Section 4.2 Table of Clinical Studies in this review summarizes the single clinical trial submitted to support the safety and efficacy of 0.5 gram (0.3 mg) Premarin® Vaginal Cream. Primary Phase 3b Study 0713S5-413-NA was used in the evaluation of efficacy. This study contributed an adequate representation for postmenopausal women.

7.2.1.1 Study type and design/patient enumeration

Refer to Section 4.2 Table of Clinical Studies for the clinical trial. This table summarizes the study design and number of subjects in each treatment group.

7.2.1.2 Demographics

The following table shows the demographic characteristics for the ITT population in Study 0713S5-413-NA.

Table 20: Summary of Demographic and Baseline Characteristics in Study 0713S5-413-NA

Characteristics	PVC 21/7 (n = 143)	Placebo 21/7 (n = 72)	PVC 2x/wk (n = 140)	Placebo 2x/wk (n = 68)	Total (n = 423)
Age (years)					
Mean ± (SD)	57.68 (5.79)	57.96 (5.76)	57.47 (5.45)	58.69 (5.81)	57.82 (5.68)
Range	44 - 77	47 – 74	45 – 75	47 – 77	44 – 77
Race, n (%)					
White	134 (93.7)	63 (87.5)	127 (90.7)	66 (97.1)	390 (92.2)
Other	9 (6.3)	9 (12.5)	13 (9.3)	2 (2.9)	33 (7.8)
Weight (kg)					
Mean ± (SD)	68.99 (15.32)	67.82 (15.04)	68.24 (12.40)	67.37 (10.06)	68.28 (13.56)
Range	44.00 – 132.81	40.20 – 122.47	46.80 – 107.50	46.27 – 99.30	40.20 – 132.81
(Missing)	(2)	(0)	(1)	(0)	(3)
Height (cm)					
Mean ± (SD)	161.55 (6.32)	160.90 (6.35)	161.54 (5.95)	162.22 (6.11)	161.54 (6.16)
Range	145.05 – 176.53	147.50 – 179.50	146.00 – 177.80	145.00 – 177.00	145.00 – 179.50
(Missing)	(2)	(0)	(1)	(0)	(3)
Years Since Last Period					
Mean ± (SD)	8.90 (5.95)	9.94 (6.69)	7.95 (5.84)	9.88 (6.70)	8.92 (6.20)
Range	0.45 – 27.34	0.98 – 30.01	0.59 – 31.16	1.11 – 31.43	0.45 – 31.43
(Missing)	(8)	(5)	(5)	(1)	(19)

Source: Modified Table 8-3: Summary of Demographic and Baseline Characteristics: Safety Population; 4-Month Safety Update received January 25, 2008.

Abbreviations: PVC = Premarin® Vaginal Cream; PVC 21/7 = apply PVC daily for 21 days, then 7 days off; Placebo 21/7 = apply placebo daily for 21 days, then 7 days off; PVC 2x/wk = apply PVC twice a week; Placebo 2x/wk = apply placebo twice a week; SD = Standard deviation.

Medical Officer's Comments:

Overall, the treatment groups in Study 0713S5-413-NA were similar with respect to demographics and baseline characteristics.

7.2.1.3 Extent of exposure (dose/duration)

A total of 423 subjects received at least 1 dose of study medication and were included in all safety analyses. Descriptive statistics for the extent of exposure and presented in Table 21.

Table 21: Mean Number of Doses of Study Medication by Week

Treatment	Treatment Duration	Number of Subjects	Mean Number of Doses (Standard Deviation)
PVC 21/7	Week 1 - 12	124	5.60 (1.82)
	Week 13 - 52	116	4.74 (1.04)
	Week 1 - 52	143	4.17 (1.66)
Placebo 21/7	Week 1 - 12	64	5.59 (1.51)
	Week 13 - 52	64	4.90 (0.89)
	Week 1 - 52	72	4.62 (1.31)
PVC 2x/wk	Week 1 - 12	123	2.01 (0.53)
	Week 13 - 52	121	1.86 (0.37)
	Week 1 - 52	140	1.71 (0.62)
Placebo 2x/wk	Week 1 - 12	65	2.00 (0.51)
	Week 13 - 52	60	1.86 (0.34)
	Week 1 - 52	68	1.73 (0.52)

Source: Adapted from sNDA 20-216/SE2-060, 4-Month Safety Update, Supportive Table 15.19.
Abbreviations: PVC = Premarin® Vaginal Cream; PVC 21/7 = apply PVC daily for 21 days, then 7 days off; Placebo 21/7 = apply placebo daily for 21 days, then 7 days off; PVC 2x/wk = apply PVC twice a week; Placebo 2x/wk = apply placebo twice a week.

Medical Officer's Comments:

Table 21 shows consistency between the treatment groups.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

In Phase 1 Study 0713S5-414-US, 24 subjects were exposed to 7 days of 0.5 g (0.3 mg) PVC and 7 days of 0.3 mg Premarin® Tablets. Three (3) subjects reported 4 treatment-emergent adverse

events (2 subjects during administration of PVC and 1 subject during administration of oral Premarin® as shown below:

Body System Adverse event	Vaginal Cream (n = 24)	Oral Tablet (n = 24)	Total (n – 24)
Abdominal discomfort	1 (4.2%)	0 (0)	1 (4.2%)
Abdominal tenderness	1 (4.2%)	0 (0)	1 (4.2%)
Muscle cramp	1 (4.2%)	0 (0)	1 (4.2%)
Breast swelling	0 (0)	1 (4.2%)	1 (4.2%)

No deaths occurred in Study 0713S5-414-US. There were no discontinuations from the study.

Medical Officer's Comments:

The treatment-emergent adverse events reported in Study 0713-414-US are known to occur with both oral and topical estrogens.

7.2.2.2 Postmarketing experience

Premarin® Vaginal Cream has been marketed for over 50 years. Postmarketing safety information has been provided proactively by Wyeth Pharmaceuticals Inc. through annual report submissions and labeling updates.

7.2.2.3 Literature

The published literature has extensively documented the potential risk and benefits of estrogen and estrogen plus progestin therapy for the treatment of vasomotor symptoms and symptoms of vulvar and vaginal atrophy associated with the menopause. These publications have raised appropriate safety concerns regarding both dose and duration of hormone therapy for menopausal symptoms. See page 14 for the review of findings of the National Institutes of Health (NIH) Women's Health Initiative (WHI) studies.

7.2.3 Adequacy of Overall Clinical Experience

A total of 423 subjects participated in the double-blind phase of Study 0713S5-413-NA During the 12-week double-blind phase, 143 subjects received PVC 21/7 (72 subjects received matching placebo) and 140 subjects received PVC 2x/wk (68 subjects received matching placebo).

A total of 394 subjects participated in the open-label phase of Study 0713S5-413-NA. During the 40-week open-label phase, all subjects received PVC. Those subjects randomized to placebo 21/7 at baseline were switched to PVC 21/7 during weeks 13-52. Likewise, those subjects randomized to placebo 2x/wk at baseline were switched to PVC 2x/wk during weeks 13-52. In

total, 198 subjects received PVC 21/7 and 196 received PVC 2x/wk during this 40-week open-label phase of Study 0713S5-413-NA.

Medical Officer's Comments:

The 423 subjects participating in 52-week, Phase 3b Study 0713S5-413-NA provided adequate safety information to demonstrate the safety of the 0.3 mg (0.5 gram) Premarin® Vaginal Cream twice weekly and daily (21 days of treatment followed by 7 days of no treatment) dosing regimens.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was conducted or required for Premarin® Vaginal Cream. It is recognized that long-term continuous administration of estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testes, and liver.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing conducted in Study 0713S5-413-NA, and the efforts to elicit adverse event data, were adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Section 5 of this review gives a brief summary of the clinical pharmacology for conjugated estrogens. See the Clinical Pharmacology and Pharmacokinetics Review for a more complete discussion. The metabolism and excretion of estrogen drug products are sufficiently understood to ease concerns about safety problems in patients with impaired excretory or metabolic function and problems resulting from drug-drug interactions.

In vitro and in vivo studies of other estrogen drug products have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations, phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effect and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects. None of these issues raised concerns that require further testing for conjugated estrogens. No further testing for these previously well defined drug interactions with conjugated estrogens are required.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The gynecologic safety data submitted is generally adequate. Wyeth Pharmaceuticals, Inc. was requested to provide additional selective endometrial hyperplasia safety information. The Applicant responded promptly with the requested information. The safety data submitted with the sNDA and the additional information on endometrial safety provided by the Applicant on request of the Agency were sufficiently adequate for the evaluation of potential adverse events.

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of the safety data submitted with sNDA 20-216/SE2-060 for the safety cohort of 423 postmenopausal women with uteri was adequate. Phase 3b, 52-week Study 0713S5-413-NA fulfills the Agency's requirement to conduct a 12-week safety and efficacy study for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. The first 12 weeks were double-blind and placebo-controlled. In addition, Study 0713S5-413-NA provided safety data regarding the use of unopposed estrogen in a woman with a uterus over a 40-week and a 52-week treatment duration.

7.2.9 Additional Submissions, Including Safety Update

A 4-Month Safety Update was submitted on January 25, 2008 which included the final report for the full 52 weeks of Study 0713S5-413-NA.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Drug-related adverse events have been discussed previously in Section 7.1.3 "Dropouts and Other Significant Adverse Events", Sub-section 7.1.3.3 "Other Significant Adverse Events". Refer to these sections for information on selected drug-related adverse events.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

In the submission, the Applicant provided Premarin® Vaginal Cream safety data based on individual dosage strengths utilized during the Premarin® Vaginal Cream development program.

The primary Phase 3b Study 0713S5-413-NA was reviewed by this reviewer.

7.4.1.2 Combining data

No data was combined in this submission.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The issue of dose dependency of reported adverse events has been discussed in several sections of this review, particularly in Section 7.1.2 "Other Serious Adverse Event", and Section 7.1.3 "Dropouts and Other Significant Adverse Events".

Medical Officer's Comments:

In the 12-week double-blind phase of Study 0713S5-413-NA, the incidence of breast pain reported in the PVC 21/7 treatment group was approximately twice that reported in the PVC 2x/wk treatment group. However, the incidence of headache in the PVC 2x/wk treatment group was approximately twice that reported in the PVC 21/7 treatment group.

Except as noted above, similar incidences of adverse events were reported across the 4 treatment groups.

7.4.2.2 Explorations for time dependency for adverse findings

Exploration of time-dependent adverse event in 52-week Study 0713S5-413-NA did not demonstrate any positive associations. The use of unopposed estrogen in a woman with a uterus increases the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

No cases of endometrial hyperplasia or endometrial cancer were reported in Study 0713S5-413-NA.

7.4.2.3 Explorations for drug-demographic interactions

No drug-demographic interactions were studied in the Premarin® Vaginal Cream clinical development program.

7.4.2.4 Explorations for drug-disease interactions

Per the submission, no drug-disease interactions were studied in the Premarin® Vaginal Cream clinical development program.

7.4.2.5 Explorations for drug-drug interactions

No drug-drug interactions were studied in the Premarin® Vaginal Cream clinical development program.

7.4.3 Causality Determination

See Subsection 7.1.3.3 "Other significant adverse events" for information regarding endometrial thickness (page 58) and endometrial biopsy (page 61), proliferative endometrium (page 63) and Premarin® Vaginal Cream use.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

For the "treatment of vulvar vaginal atrophy (VVA), dyspareunia associated with VVA or kraurosis vulvae", the Applicant is requesting approval of two 0.5 gram (0.3 mg) dosing regimens of Premarin® Vaginal Cream

8.2 Drug-Drug Interactions

No drug-drug interactions studies were performed as part of the Premarin® Vaginal Cream development program.

8.3 Special Populations

No pharmacokinetic studies were conducted in special populations, including subjects with renal or hepatic impairment.

Based on data from comparable estrogen therapy products, no formal studies in humans on the effect of Premarin® Vaginal Cream on reproduction or pregnancy were performed. Similarly, no information on drug exposure in pregnant women, including any inadvertent exposure during drug development, was identified.

8.4 Pediatrics

Premarin® Vaginal Cream is not indicated for use in a pediatric population.

8.5 Advisory Committee Meeting

There was no advisory committee meeting in which Premarin® Vaginal Cream was discussed.

8.6 Literature Review

Literature relevant to estrogen therapy has been referenced in this review as needed. There is no need for a separate comprehensive review of the literature.

8.7 Postmarketing Risk Management Plan

There is no need for a postmarketing risk management plan.

8.8 Other Relevant Materials

There are no relevant materials that are not included in other sections of this review. The results of a review of the product name from the Division of Medication Errors Prevention (DMEDP) in the Office of Surveillance and Epidemiology (OSE) is discussed in Section 2.1 of this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

9.2 Recommendation on Regulatory Action

The reviewer recommends approval of 0.3 mg Premarin® Vaginal Cream (0.5 gram containing 0.625 mg of conjugated estrogens per gram of cream) inserted vaginally twice weekly (for example, Monday and Thursday) for the treatment of moderate to severe pain associated with sexual activity (dyspareunia) due to menopause. This reviewer also recommends approval of 0.3 mg Premarin® Vaginal Cream inserted daily for 21 days, then off for 7 days for the treatment of moderate to severe dyspareunia due to menopause.

Sufficient evidence is provided in the application to conclude that 0.3 mg Premarin® Vaginal Cream inserted vaginally twice weekly or daily for 21 days, then off for 7 days provides relief in the treatment of moderate to severe dyspareunia due to menopause. The safety of this product is not a major concern. The reported serious and common adverse events are consistent with other intravaginal estrogen hormone products approved to treat moderate to severe symptoms of vulvar and vaginal atrophy due to menopause.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No postmarketing risk management activities are recommended.

9.3.2 Required Phase 4 Commitments

No Phase 4 clinical study commitment is proposed.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests.

9.4 Labeling Review

The following are the reviewer's recommended Structured Product Labeling (SPL) changes for PVC labeling. In the PVC labeling, changes are presented in the format required by 21 CFR 314.50(1)(i) and (1)(5) and 314.71(b); see also Memorandum 32 to Docket Number 92S-0251 for the specific requirements on content and format of labeling for human prescription drugs, and on the Agency's Guidance for Industry, *Providing Regulatory Submissions in Electronic Format – Content of Labeling* and 21 CFR Parts 201, 314, and 601 Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products (71 FR 3992).

Highlights Section of Prescriber Labeling:

Boxed Warning: Information has been summarized in a bulleted format. The boxed warning has been updated not to exceed a length of 20 lines.

Recent Major Changes: Section identifies changes to approved labeling in March 2008.

Indications and Usage: Text modified to read, "Premarin Vaginal Cream is an estrogen indicated in the treatment of moderate to severe vulvar and vaginal atrophy and moderate to severe dyspareunia, symptom of vulvar and vaginal atrophy, due to menopause".

Warnings and Precautions: Summary statements of the most clinically significant information included.

Full Prescribing Information:

(b) (4)

(b) (4)

Patient Information Leaflet:

(b) (4)

9.5 Comments to Applicant

Premarin® Vaginal Cream 0.3 mg (0.5 gram containing 0.625 mg of conjugated estrogens per gram of cream) inserted vaginally twice weekly (for example, Monday and Thursday) and Premarin® Vaginal Cream 0.3 mg (0.5 gram containing 0.625 mg of conjugated estrogens per gram of cream) inserted daily for 21 days, then off for 7 days are approved for the treatment of moderate to severe dyspareunia, symptom of vulvar and vaginal atrophy, due to menopause.

APPENDICES

9.6 Review of Individual Study Reports

The review of the single Phase 3b Study 0713S5-413-NA is included in this review.

9.7 Line-by-Line Labeling Review

See final agreed upon labeling.

REFERENCES

1. Rossouw, JE, et al. Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause. JAMA. 2007;297:1465-1477.

2. Hsia J, et al. Conjugated Equine Estrogens and Coronary Heart Disease. Arch Int Med. 2006;166:357-365.

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5. Heiss G, et al. Health Risks and Benefits 3 Years After Stopping Randomized Treatment With Estrogen and Progestin. JAMA. 2008;299:1036-1045.

6. Jackson RD, et al. Effects of conjugated Equine Estrogen on Risk of Fractures and BMD in Postmenopausal Women With Hysterectomy: Results From the Women's Health Initiative Randomized Trial. J Bone Miner Res 2006;21:817-828.

7. Hendrix SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative. Circulation. 2006;113:2425-2434.

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/s/

Theresa Van Der Vlugt
7/24/2008 01:18:02 PM
MEDICAL OFFICER

Shelley Slaughter
7/24/2008 03:10:51 PM
MEDICAL OFFICER
I concur with Dr. van der Vlugt regarding approvability and recommend Approvable pending acceptance of a final agreed upon label. See MO Team Leader memo.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20216Orig1s060

CHEMISTRY REVIEW(S)

Office of New Drug Quality Assessment (ONDQA)
Division of Post-Marketing Evaluation
Chemistry Review

For Clinical Division: Reproductive and Urologic Drug Products

NDA 20-216

Efficacy supplement SE2-060
Date of original submission: 25-Sept-2007
Date of Resubmission: 5-Sept-2008

Document reviewed:
5-Sept-2008 Class 1 Resubmission

Review Date: 4-Nov-2008
Chemistry Reviewer: Jean Salemme, Ph.D.

Background

Efficacy supplement NDA 20-216 SE2 060 for Premarin (conjugated estrogens) Vaginal Cream was submitted 25-Sept-2007. The efficacy supplement proposes a new dosage regimen for Premarin Vaginal Cream, from daily use for 21 days followed by 7 days off to the proposed dosage of 0.5 g twice weekly. No changes are proposed in the approved chemistry, manufacturing and controls.

See Chemistry review #1 of the supplement for an evaluation of the Environmental Assessment, and for statements that no changes were made to the How Supplied and Description sections of the label submitted with the original supplement.

Supplement 20-216 SE2 060, which received an Approvable Action for clinical reasons, was resubmitted 5-Sept-2008.

Chemistry Review of 5-Sept-2008 Resubmisison **Acceptable**

The label provided in the resubmitted supplement, dated 5-Sept-2008, has been reviewed. No changes have been made to the HOW SUPPLIED and DESCRIPTION sections of the label. The label, therefore, is acceptable from a CMC perspective.

Signed: Dr. J. Salemme, Chemistry Reviewer, ONDQA-DPE, 4-Nov-2008
Reviewed : Dr. Hasmukh Patel, Branch Chief, Branch VIII, Division IV, ONDQA

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/s/

Jean Salemme
11/4/2008 12:28:01 PM
CHEMIST

Hasmukh Patel
11/4/2008 12:33:27 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20216Orig1s060

ENVIRONMENTAL ASSESSMENT

Office of New Drug Quality Assessment (ONDQA)
Division of Post-Marketing Evaluation
Chemistry Review

For Clinical Division: Reproductive and Urologic Drug Products

NDA 20-216

Efficacy supplement SE2-060
Date of submission: 25-Sept-2007

Document reviewed:
9-Nov-2007 Environmental Assessment

Review Date: 19-Mar-2008
Chemistry Reviewer: Jean Salemme, Ph.D.

Efficacy supplement SE2 060 to NDA 20-216 Premarin (conjugated estrogens) Vaginal Cream was submitted 25-Sept-2007. The supplement proposes a new dosage regimen for Premarin Vaginal Cream, from daily use for 21 days followed by 7 days off, to the proposed dosage of 0.5 g twice weekly.

1

Chemistry Review

For supplement 20-216 / SE2 060, no changes are proposed in the approved chemistry, manufacturing and controls. Additionally, no changes have been made to the chemistry sections of the label.

An Environmental Assessment (EA) section has been provided and is evaluated as follows:

Environmental Assessment (9-Nov-2007 submission)

The sponsor provides statements that the proposed supplement for a lower dosage regimen will not increase the use of the active moiety. Therefore, an Environmental Assessment to address an increased amount of active is not required, according to 21CFR 25.31(a).

Evaluation: Acceptable. The request for exclusion from the requirement for an Environmental Assessment is justified.

Signed: Dr. J. Salemme, Chemistry Reviewer, ONDQA-DPE, 19-Mar-2008
Reviewed : Dr. Hasmukh Patel, Branch Chief, Branch VIII, Division IV, ONDQA

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/s/

Jean Salemme
3/19/2008 12:10:52 PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20216Orig1s060

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	20-216
SERIAL NUMBER:	S-60 (Class 1 resubmission)
DATE RECEIVED BY CENTER:	11-2-08
PRODUCT:	Premarin vaginal cream
INTENDED CLINICAL POPULATION:	Treatment of valvar vaginal atrophy, dydpareunia associated with VVA or Kraurosis
SPONSOR:	Wyeth Pharmaceuticals Inc. Philadelphia, PA**xxxxxx**
DOCUMENTS REVIEWED:	Draft Label 01Nov08 Wyeth response.
REVIEW DIVISION:	DRUP (HFD-580)
PHARM/TOX REVIEWER:	Krishan L. raheja, D.V.M., Ph.D.
PHARM/TOX SUPERVISOR:	Lynnda Reid, Ph.D.
DIVISION DIRECTOR:	Scott Monroe, M.D.
PROJECT MANAGER:	George Lyght

Date of review submission to Division File System (DFS): 11-4-08

Recommendations on Labeling: Pharmacology/Toxicology review of original NDA submission dated 9-25-07 entered in DFS on 10-9-07 remains unchanged. The label is acceptable from the P/T perspective.

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/s/

Krishan L. Raheja
11/4/2008 10:31:26 AM
PHARMACOLOGIST

Lynnda Reid
11/4/2008 10:34:48 AM
PHARMACOLOGIST
I concur with the following: 1) Nonclinical data support approval; 2) Labeling is acceptable.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	20-216
SERIAL NUMBER:	SE2-060
DATE RECEIVED BY CENTER:	9/25/07
PRODUCT:	Premarin Vaginal Cream (Conjugated estr (b) (4)
INTENDED CLINICAL POPULATION:	treatment of vulvar vaginal atrophy (VVA), dyspareunia associated with VVA or kraurosis.
SPONSOR:	Wyeth Pharmaceuticals Inc. Philadelphia, PA
DOCUMENTS REVIEWED:	An electronic submission
REVIEW DIVISION:	Division of Reproductive and Urologic Drug Products
(HFD-)	580
PHARM/TOX REVIEWER:	Krishan L. Raheja, D.V.M., Ph.D.
PHARM/TOX SUPERVISOR:	Lynnda Reid, Ph.D.
DIVISION DIRECTOR:	Scott Monroe, M.D.
PROJECT MANAGER:	George Lyght

Date of review submission to Division File System (DFS): 10-9-07

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Nonclinical data support approval

B. Recommendation for nonclinical studies: No new clinical studies are required. All have been reviewed under sponsor's original IND 72,606 and approved NDA 20-216 for Premarin Vaginal Cream. The purpose of this submission is to support a new dosing regimen option, 0.5 g twice weekly of Premarin Vaginal Cream (PVC) for the treatment of vulvar vaginal atrophy (VVA), dyspareunia associated with VVA or kraurosis vulvae. The currently approved dosage for PVC for the treatment of atrophic vaginitis or kraurosis vulvae is 0.5 g – 2 g cyclically (e.g., three weeks on and one week off).

C. Recommendations on labeling: Sponsor has proposed acceptable revised labeling in PLR format.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings; No adverse findings.

B. Pharmacologic activity: Estrogenic activity

C. Nonclinical safety issues relevant to clinical use: None

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/s/

Krishan L. Raheja
3/6/2008 08:48:57 AM
PHARMACOLOGIST

Lynnda Reid
3/6/2008 01:54:54 PM
PHARMACOLOGIST
There is no new nonclinical data. Previous nonclinical data supports approval.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20216Orig1s060

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	NDA 20-216, Supplement
Drug Name:	Premarin Vaginal Cream
Indication(s):	Treatment of atrophic vaginitis and kraurosis vulvae
Applicant:	Wyeth
Date(s):	Submitted 9/5/2008
Review Priority:	Resubmission, 60 days
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Lisa A. Kammerman, Ph.D.
Concurring Reviewers:	Mahboob Sobhan, Ph.D.
Medical Division:	Reproductive and Urologic Products, HFD-180
Clinical Team:	Theresa van der Vlugt, MD
Project Manager:	George Lyght

Keywords: clinical studies

NDA 20-216, Supplement 060 was submitted on 9/25/07. This resubmission does not contain new clinical data. Therefore, my statistical review of the original supplement, submitted 9/25/07, remains unchanged.

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/s/

Lisa A. Kammerman
11/4/2008 10:32:39 AM
BIOMETRICS

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	NDA 20-216, Supplement 060
Drug Name:	Premarin Vaginal Cream
Indication(s):	Treatment of atrophic vaginitis and kraurosis vulvae
Applicant:	Wyeth
Date(s):	Submitted 9/25/07
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Lisa A. Kammerman, Ph.D.
Concurring Reviewers:	Mahboob Sobhan, Ph.D.
Medical Division:	Reproductive and Urologic Products, HFD-180
Clinical Team:	Theresa van der Vlugt, MD
Project Manager:	George Lyght

Keywords: clinical studies

Table of Contents

LIST OF TABLES

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The results support the efficacy of 0.5 g of Premarin Vaginal Cream (conjugated estrogens 0.625 mg/g) administered in two regimens in their ability to reduce the severity of dyspareunia among healthy post-menopausal women with moderate-to-severe vaginal atrophy. The two regimens are (1) 0.5 g of Premarin Vaginal Cream (conjugated estrogens 0.625 mg/g) administered once daily for 21 days and off for 7 days (PVC 21/7) and (2) 0.5 g of Premarin Vaginal Cream (conjugated estrogens 0.625 mg/g) administered twice weekly (PVC 2x/wk). The results for vaginal burning, vaginal dryness and vaginal itching were not statistically significant.

Further, vaginal pH and the percentage of parabasal cells were decreased significantly among women treated with either PVC 21/7 or PVC 2x/wk as compared with women treated with placebo. The percentage of superficial cells was increased significantly among women treated with either active treatment as compared with women treated with placebo.

I recommend that labeling includes results from the analyses of the overall study population and not the results from per protocol analyses. This approach is consistent with the intent-to-treat principle. At best, the per protocol analysis can be considered to be a sensitivity analysis.

1.2 Brief Overview of Clinical Studies

The submission contains a single study to support the efficacy for the proposed dosage regimen of 0.5 gm twice weekly:

> Protocol 0713S5-413-NA: "Efficacy and Safety of 2 Low-Dose Regimens of Conjugated Estrogen Cream Administered Vaginally in Postmenopausal Women with Atrophic Vaginitis"

The study enrolled 431 postmenopausal women, of whom 423 took at least one dose of treatment. The study was multicenter, double-blind, randomized, placebo-controlled and was conducted at 49 sites in Canada and the United States. The study evaluated the efficacy and safety of a low-dose (conjugated estrogens 0.3 mg) of PVC (conjugated estrogens 0.625 mg/g) administered by 1 of 2 dose regimens for 12 weeks: the approved regimen (once daily for 21 days, off for 7 days [PVC-21/7]) and an intermittent regimen (twice weekly [PVC-2x/week]). Each regimen was compared with its corresponding placebo group. Subjects were randomized in a 2:1 ratio of treatment:placebo.

The entry criteria called for healthy, postmenopausal women, 45 to 80 years old, with an intact uterus and signs and symptoms consistent with moderate to severe vaginal atrophy.

The primary endpoints were changes in percentages of superficial and parabasal cells, vaginal pH, and most bothersome symptom as compared with placebo at Week 12 of treatment.

1.3 Statistical Issues and Findings

For the composite endpoint of change from baseline to Week 12 for the most bothersome symptom, the results showed statistically significant differences between each active treatment and its matching placebo. However, when the components of this composite endpoint were examined, dyspareunia was identified as the symptom accounting for the treatment differences. Of the four possible most bothersome symptoms (dyspareunia, vaginal burning, vaginal dryness and vaginal itching), dyspareunia was the only one demonstrating statistically significant improvements among those randomized to active treatment as compared to those randomized to the matching placebo.

The Medical Officer requested the applicant to submit a per protocol analysis of the individual symptoms among subjects who had a baseline pH of 5 or greater, who had not more than 5 percent superficial cells on a vaginal smear at baseline, and whose most bothersome baseline symptom had a severity score of at least 2. This request eliminated 37 subjects. The results from this per protocol analysis were consistent with those from the larger population. In their response to this request, the applicant submitted analyses that were adjusted for baseline severity score. All other analyses in the original submission are adjusted for baseline score and study site, which is the statistical methodology specified in the protocol and statistical analysis plan.

2. INTRODUCTION

2.1 Overview

Premarin Vaginal Cream (PVC) is approved for the treatment of atrophic vaginitis. The approved dosage is 0.5 gm – 2 gm applied daily for 21 days followed by 7 days (b) (4) (21/7). The applicant is seeking approval for a new dosage regimen of 0.5 gm twice weekly.

In addition to showing efficacy of the new regimen, the applicant is evaluating the efficacy of the currently marketed regimen of 0.5 gm applied daily for 21 days followed by 7 days (b) (4), which was marketed under DESI.

The submission contains a single study to support the new regimen:

> Protocol 0713S5-413-NA: "Efficacy and Safety of 2 Low-Dose Regimens of Conjugated Estrogen Cream Administered Vaginally in Postmenopausal Women with Atrophic Vaginitis"

The study was conducted at 49 sites in the United States and Canada. A total of 431 subjects were randomized in a 2:1 (PVC-to-Placebo) ratio to one of four treatment groups and treated for 12 weeks:

- 0.3 mg (0.5 gm) PVC daily for 21 days, 7 days off (n=145)
- 0.5 gm placebo cream daily for 21 days, 7 days off (n= 72)
- 0.3 mg (0.5 gm) PVC twice weekly (n=141)
- 0.5 gm placebo cream twice weekly (n= 73)

Eight of these subjects did not take any study treatment or did not return to the clinic. They are not included in the analyses of efficacy or safety.

The inclusion criteria specified post-menopausal women with signs and symptoms consistent with moderate to severe vaginal atrophy, 0% to 5% superficial cells, and an intact uterus.

The protocol specified three co-primary endpoints:

- Change from baseline in VMI (% superficial and parabasal cells) at Week 12
- Change from baseline in vaginal ph at Week 12
- Change from baseline in severity of most bothersome vaginal symptom at Week 12

The prespecified analysis was analysis of covariance (ANCOVA) with treatment group and center as factors and the corresponding baseline value as a covariate. The baseline symptom score is the average score across all scores prior to randomization. For all other variables, the last value recorded prior to randomization was the baseline value.

Each active treatment was compared with its corresponding placebo group:

- 0.3 mg (0.5 gm) PVC daily for 21/7 *versus* 0.5 gm placebo cream daily for 21/7
- 0.3 mg (0.5 gm) PVC twice weekly *versus* 0.3 mg (0.5 gm) placebo cream twice weekly

2.2 Data Sources

Efficacy Supplement dated 9/25/07 (20-216/S-060; eCTD Sequence 0006)
\\Cdsesub1\evsprod\NDA020216\0006\m5

Amendment dated 12/13/07: Response to Information Request dated 11/15/07 (20-216/S-060; eCTD Sequence 0012)
\\CDSESUB1\EVSPROD\NDA020216\\0012\m5\53-clin-stud-rep\535-rep-effic-safety-stud\atrophic-vaginitis-and-kraurosis-vulvae\5351-stud-rep-contr\study-0713s5-413\csr67635-report-body.pdf

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

Study 0713S5-413-NA, "Efficacy and Safety of 2 Low-Dose Regimens of Conjugated Estrogen Cream Administered Vaginally in Postmenopausal Women with Atrophic Vaginitis," was a multicenter, double-blind, randomized, placebo-controlled study conducted at 49 sites in the United States and Canada.

Healthy, postmenopausal women, 45 to 80 years old, with an intact uterus, 0% to 5% superficial cells, and with moderate to severe vaginal atrophy were eligible for the study. Moderate to severe vaginal atrophy was defined as a baseline composite score of at least 5 (1 = mild, 2 = moderate, 3 = severe) for the symptoms of vaginal dryness, itching, burning, and dyspareunia; a total score of ≤15 on the GHCE; and a vaginal pH of ≥5.

A total of 742 subjects were screened and 431 were randomized in a 2:1 (PVC-to-Placebo) ratio to one of four treatment groups (Table 1).

Table 1. Number of subjects randomized and included in the MITT population.

Treatment Group	Randomized (n=431)	Modified ITT Population (n=423)
0.3 mg (per 0.5 gm of cream) PVC daily for 21 days, 7 days off	145	143
0.5 gm placebo cream daily for 21 days, 7 days off	72	72
0.3 mg (per 0.5 gm of cream) PVC twice weekly	141	140
0.5 gm placebo cream twice weekly	73	68

Eight subjects did not take any study treatment or did not return to the clinic. They are not included in the analyses of efficacy or safety. The remaining 423 subjects constitute the modified intent to treat analysis (MITT) population, defined as all randomized subjects who took at least one dose of treatment, had a baseline value and at least one follow-up visit (Table 1). The MITT population is smaller for analyses of some of the individual endpoints, depending on whether there is a follow-up visit or not for that endpoint. Dyspareunia is the endpoint most affected, because it cannot be assessed if a woman did not have sexual intercourse. Last observation carried forward (LOCF) was used for subjects who did not complete 12 weeks.

Subjects were to receive 12 weeks of blinded treatment followed by an additional 40 weeks in an open-label safety study in which everyone received active treatment. During the double-blind phase of the study, subjects were to return at Weeks 4, 6 and 12 for efficacy and safety assessments. Subjects received a 100 day supply of study medication at the time of randomization.

The protocol specified three co-primary endpoints:

- Change from baseline in VMI (% superficial and parabasal cells) at Week 12
- Change from baseline in vaginal pH at Week 12
- Change from baseline in severity of most bothersome vaginal symptom at Week 12

VMI was assessed by a vaginal cytologic smear. Vaginal pH was assessed during a genital examination.

Symptoms were assessed daily using daily diary cards, starting at screening. The symptoms included vaginal dryness, itching, burning, and dyspareunia. Subjects were to score each of the symptoms daily: 0 = none, 1= mild, 2 = moderate, 3 = severe, 5 = not applicable and 9 = not done. Weekly symptom scores were derived from the average of all daily scores recorded during a 7-day period (excluding scores of 5 and 9). A subject's most bothersome symptom was the one she identified at screening. This symptom was used to define one of the primary endpoints of the study.

The prespecified analysis was analysis of covariance (ANCOVA) with treatment group and center as factors and the corresponding baseline value as a covariate. The baseline symptom score is the average score across all scores prior to randomization. For all other variables, the last value recorded prior to randomization was the baseline value. Last observation carried forward (LOCF) was used for subjects who did not complete 12 weeks.

Each active treatment was compared with its corresponding placebo group:

- 0.3 mg (0.5 gm) PVC daily for 21/7 ***versus*** 0.5 gm placebo cream daily for 21/7
- 0.3 mg (0.5 gm) PVC twice weekly ***versus*** 0.3 mg (0.5 gm) placebo cream twice weekly

3.1.2 Description of Subjects

Of the 423 subjects who took at least 1 dose of study medication, 394 (93.1%) completed the double-blind phase. The highest discontinuation rate (9.8%) occurred among the PVC 21/7 treatment group, due primarily to adverse events. The lowest discontinuation rate (4.2%) occurred among the Placebo 21/7 treatment group. The twice a week regimens had essentially the same rates of discontinuations, approximately 6%. The following table summarizes the discontinuations (Table 2):

Table 2. Summary of discontinuations among the MITT population (n=423)

Conclusion Status Reason[a]	Treatment Sequence: PVC 21/7 n=143	Placebo 21/7 n=72	PVC 2x/wk n=140	Placebo 2x/wk n=68	Total n=423
Discontinued	14 (9.8)	3 (4.2)	8 (5.7)	4 (5.9)	29 (6.9)[b]
Adverse Event	6 (4.2)[b]	1 (1.4)	4 (2.9)	2 (2.9)	13 (3.1)[b]
Lost to Follow-up	1 (0.7)	0	0	1 (1.5)	2 (0.5)
Protocol Violation	1 (0.7)	0	1 (0.7)	0	2 (0.5)
Subject Request	6 (4.2)	2 (2.8)	3 (2.1)	1 (1.5)	12 (2.8)

a. Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.
b. Subject (b) (6) in the PVC 21/7 treatment group, who withdrew because of an AE (intermittent headaches), was omitted from the clinical data report. (See section 14.0 Errata). Her withdrawal is included in this table and the totals reflect this change.

Source R&D/CLINICAL PROGRAMMING SAS REPORTS/0713S5 /P413_INTERIM/Intext/ 0713-P413_INTERIM CPP-5_STUDY_DB - 18APR07 10:33, and 14.0 CLINICAL DATA REPORT ERRATA

Source: Table 8-1, Interim Clinical Study Report dated 8/3/07

Overall, the average age of the women enrolled in the study was 58 years, with a range of 44 to 77 years. Most were white (92%) and 5% were Hispanic or Latino.

Approximately 75% of the subjects were included in the applicant's analyses of the most bothersome symptom. Most of those who were not included reported dyspareunia as their most bothersome symptom at screening, but listed "not applicable" for that symptom during the screening period or the treatment phase of the study. This would occur if the woman did not have sexual intercourse during the reporting windows.

3.1.3 Results

3.1.3.1 Most Bothersome Symptom

Among the 412 subjects who reported a most bothersome symptom at baseline, the most common complaint was painful intercourse, followed by vaginal dryness (Table 3). Vaginal itching and vaginal burning were the least common symptoms.

Table 3. Distribution of symptoms selected as most bothersome at baseline, by number (%) of subjects and treatment group.

Symptom	Treatment: PVC 21/7 n=138	Placebo 21/7 n=70	PVC 2x/wk n=137	Placebo 2x/wk n=67
Vaginal Dryness	34 (24.64)	21 (30.00)	32 (23.36)	16 (23.88)
Vaginal Itching	7 (5.07)	11 (15.71)	12 (8.76)	9 (13.43)
Vaginal Burning	9 (6.52)	5 (7.14)	10 (7.30)	5 (7.46)
Painful Intercourse	88 (63.77)	33 (47.14)	83 (60.58)	37 (55.22)

Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/0713S5 Premarin Vaginal Cream/P413/ Eff_Tab_Gen_MB_Sum.rtf - Jun 8, 2007 3:36:19 PM (Date and Time: Modified in EDMS)

Source: Table 9-6, Interim Clinical Study Report dated 8/3/07

When compared with their respective placebo groups, the reduction in the symptom score at Week 12 for the most bothersome symptom was statistically significant for each of the active treatment groups ($p<0.001$). Table 4 shows the results for those subjects with at least one follow-up visit.

Table 4. Summary of least-squared means (standard error) in the change from baseline to Week 12 for the most bothersome symptom, for subjects with at least one follow-up visit. Each comparison of the active treatment with its placebo is statistically significant ($p<0.001$). Means are adjusted for study site and baseline value.

Treatment			
PVC-21/7 (n=101)	Placebo-21/7 (n=56)	PVC-2x/wk (n=107)	Placebo-2x/wk (n=52)
-1.27 (0.10)	-0.75 (0.13)	-1.37 (0.10)	-0.72 (0.14)

Source: Table 2-5, Summary of Clinical Efficacy[1] *and Statistical Reviewer's analysis*

The statistically significant differences between active treatment and its matching placebo were due to dyspareunia (Table 5). For each of the other three symptoms, there was no statistically significant difference between treatment and placebo. The statistically significant difference would have remained significant if a Bonferroni adjustment for multiple comparison had been made.

With 95% confidence, the true change from baseline to Week 12 in the symptom score for dyspareunia could be from .60 to 1.70 symptom score units better for PVC 21/7 than for Placebo 21/7; and from .34 to 1.42 units better for PVC 2x/week than for Placebo 2x/week (Table 6).

[1] The sample sizes reported in Table 2-5, Summary of Clinical Efficacy are incorrect, most likely due to a transcription error. I was able to reproduce the mean changes and standard errors.

Table 5 Results of ANCOVA and summary of least-squared means (standard error) in the change from baseline at Week 12, by each symptom reported as most bothersome symptom at baseline. Comparison of the active treatment with its placebo is statistically significant (p<0.002) for dyspareunia only. Means are adjusted for study site and baseline value.

Symptom	n	PVC 21/7	n	Placebo 21/7	p-value	n	PVC 2x/wk	n	Placebo 2x/wk	p-value
Dyspareunia	53	-1.47 (.16)	20	-0.33 (.24)	<.001	54	-1.49 (.15)	23	-0.61 (.23)	.002
Vaginal Burning	9	-0.54 (.43)	5	-0.36 (.48)	.78	9	-0.28 (.38)	5	-1.23 (.71)	.33
Vaginal Dryness	32	-1.46 (.19)	20	-1.24 (.24)	.46	32	-1.52 (.20)	16	-1.43 (.28)	.80
Vaginal itching	7	-0.37 (.43)	11	-0.71 (.37)	.58	12	-0.85 (.34)	9	-1.07 (.47)	.72

Source: Statistical Reviewer's analyses

Table 6 Estimates of treatment effect and their 95% confidence intervals for the change from baseline at Week 12; all analyses are adjusted for study site and baseline value.

	PVC 21/7 versus Placebo 21/7		PVC 2x/wk versus Placebo 2x/wk	
Symptom	Estimate of Treatment Effect (Treatment – Placebo)	95% Confidence Interval	Estimate of Treatment Effect (Treatment – Placebo)	95% Confidence Interval
Dyspareunia	-1.14	-1.70, -0.60	-0.88	-1.42, -0.34
Vaginal Burning	-0.18	-1.67, 1.30	0.95	-1.16, 3.07
Vaginal Dryness	-0.22	-0.82, 0.38	-0.09	-.075, 0.58
Vaginal itching	0.34	-.93, 1.61	0.22	-1.06, 1.77

Source: Statistical Reviewer's analyses

Per Protocol Analysis of Symptoms

In an Information Request dated 11/15/07, the Medical Officer requested per protocol analyses of change from baseline to Week 12 for each separate symptom reported as most bothersome at baseline. These analyses are limited to the per protocol population of subjects who

- had a baseline vaginal pH of 5 or greater,

- had no more than 5 percent superficial cells on a vaginal smear ***and***
- reported a most bothersome symptom with a severity score of 2 or greater.

This per protocol population of 386 subjects, therefore, differs slightly from the population of 423 subjects summarized in Table 3 and Table 4. Of these 386 subjects, 290 met the MITT criteria for most bothersome symptom.

Table 7 reports descriptive statistics for change from baseline to Week 12 among the 290 subjects who had a baseline vaginal pH of 5 or greater, who had no more than 5 percent superficial cells on a vaginal smear, who reported a most bothersome symptom with a severity score of 2 or greater and who satisfied the MITT criteria for most bothersome symptom.

In this per protocol population, results of the analyses of covariance, adjusted for baseline severity score and study site[2], are consistent with the results from the larger population reported above in Table 5. Dyspareunia is the only symptom with statistically significant differences between active treatment and its matching placebo Table 8. A statistically significant difference between treatment and placebo did not exist for any of the other three symptoms.

With 95% confidence, the true change from baseline to Week 12 in the symptom score for dyspareunia could be from .57 to 1.74 symptom score units better for PVC 21/7 than for Placebo 21/7; and from .19 to 1.33 units better for PVC 2x/week than for Placebo 2x/week.

[2] The applicant's Response to the Information Request presents results adjusted for baseline value only; see Table 1-2, Amendment dated 12/13/07. The results are consistent with those adjusted for study site and baseline value.

Table 7. Per protocol population: mean change (standard deviation) for each symptom reported as most bothersome at baseline *among the subgroup of subjects who had a baseline vaginal pH of 5 or greater, who had ≤5% superficial cells on a vaginal smear and whose most bothersome symptom was moderate to severe.* Results are unadjusted for study site or baseline values.

	PVC 21/7 (n = 93)[a]		Placebo 21/7 (n = 51)[a]		PVC 2x/wk (n = 98)[a]		Placebo 2x/wk (n = 48)[a]	
Symptom	n[b]	Mean (SD)	n[b]	Mean (SD)	n[b]	Mean (SD)	n[b]	Mean (SD)
Dyspareunia	50	-1.48 (1.17)	18	-0.40 (1.01)	52	-1.55 (0.92)	21	-0.62 (1.23)
Vaginal Burning	7	-0.54 (0.99)	5	-0.27 (0.93)	7	-1.23 (1.34)	4	-0.66 (1.68)
Vaginal Dryness	30	-1.31 (1.06)	19	-1.28 (1.21)	27	-1.40 (0.98)	15	-1.26 (1.08)
Vaginal Itching	6	-0.63 (0.96)	9	-0.69 (0.76)	12	-0.99 (1.09)	8	-0.29 (0.84)

LOCF = last observation carried forward; MITT = modified intent-to-treat; n = number of subjects satisfying all 3 conditions; PVC = Premarin vaginal cream (0.625 mg conjugated estrogens/g cream); PVC 21/7 = apply PVC for 21 days and then 7 days of no therapy (weeks 1 to 52); PVC 2x/wk = apply PVC twice a week, continuously (weeks 1 to 52); SD = standard deviation.

a. Total number of subjects equals the sum for the 4 symptoms because each subject has only 1 most bothersome symptom.

b. Number of subjects satisfying 3 conditions: (1) Self-identified at least one moderate to severe vulvar and vaginal atrophy symptom (severity score of 2.0 or greater for vaginal dryness, vaginal itching, vaginal burning, or dyspareunia) that was also self-identified as most bothersome; (2) Had a baseline vaginal pH of 5 or greater; (3) Had no more than 5 percent superficial cells on a vaginal smear.

Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/0713S5 Premarin Vaginal Cream/P413/Regulatory/Eff_3con.htm; 28NOV07 10:25

Source: Table 1-1, Amendment dated 12/13/07

Table 8. Per protocol population: results of ANCOVA and summary of least-squared means (standard error) in the change from baseline at Week 12, by each symptom reported as most bothersome symptom at baseline *among the subgroup of subjects who had a baseline vaginal pH of 5 or greater, who had ≤5% superficial cells on a vaginal smear and whose most bothersome symptom was moderate to severe.* Comparison of the active treatment with its placebo is statistically significant (p<0.01) for dyspareunia only. Means are adjusted for study site and baseline value.

Symptom	n	PVC 21/7	n	Placebo 21/7	p-value	n	PVC 2x/wk	n	Placebo 2x/wk	p-value
Dyspareunia	50	-1.51 (.17)	18	-0.36 (.26)	<.001	52	-1.45 (.16)	21	-0.69 (.24)	.01
Vaginal Burning	7	-0.22 (.20)	5	-0.64 (.21)	.21	7	-0.64 (.21)	4	-1.39 (.31)	.15
Vaginal Dryness	30	-1.53 (.21)	19	-1.19 (.25)	.29	27	-1.60 (.23)	15	-1.56 (.30)	.91
Vaginal itching	6	-0.87 (.45)	9	-.51 (.41)	.93	12	-0.86 (.32)	8	-1.20 (.48)	.58

Source: Statistical Reviewer's analyses

These per protocol analyses can be considered to be sensitivity analyses. The results are consistent with the results from the ITT analyses.

3.1.3.2 Vaginal pH and superficial/parabasal cells

For the MITT population, the applicant reported statistically significant reductions ($p<0.001$) in vaginal pH for each active treatment group versus its placebo group. The average reduction in vaginal pH for each active treatment group was approximately 1.6 compared with .3 for each placebo treatment group. The means, which are adjusted for study site and for vaginal pH at baseline, are from analyses of 402 subjects with a follow-up assessment of vaginal pH.

The treatment effects were also statistically significant ($p<0.001$) for the increase in percentage of superficial cells at Week 12 and for the decrease in parabasal cells at Week 12. These results are from analyses of 419 subjects with follow-up assessments of superficial and parabasal cells, and are adjusted for study site and for baseline values of parabasal cells or superficial cells. The increase in superficial cells for the active treatment groups was approximately 24 percentage units greater than the increase observed for the matching placebo groups. The decrease in parabasal cells was approximate 40 percentage units greater for PVC 21/7 than for Placebo 21/7, and about 50 units greater for PVC 2x/wk than for Placebo 2x/wk.

I was able to reproduce these analyses and generate the results found in the submission.

3.2 Evaluation of Safety

See Medical Officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The applicant did not submit analyses of subgroups defined by race or age. All subjects were female.

4.2 Other Special/Subgroup Populations

None.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

For the composite endpoint of change from baseline to Week 12 for the most bothersome symptom, the results showed statistically significant differences between each active

treatment and its matching placebo. However, when the components of this composite endpoint were examined, dyspareunia was identified as the symptom accounting for the treatment differences. Of the four possible most bothersome symptoms (dyspareunia, vaginal burning, vaginal dryness and vaginal itching), dyspareunia was the only one demonstrating statistically significant improvements among those randomized to active treatment as compared to those randomized to the matching placebo. This comparison would have been statistically significant if a Bonferroni adjustment for multiple comparisons had been made.

The Medical Officer requested analyses of the individual symptoms among the per protocol population of subjects who had a baseline pH of 5 or greater, who had not more than 5 percent superficial cells on a vaginal smear at baseline, and whose most bothersome baseline symptom had a severity score of at least 2. This request eliminated 37 subjects. The results were consistent with those from the larger population.

In their response to this request, the applicant submitted analyses that were adjusted for baseline severity score. All other analyses in the original submission are adjusted for baseline score and study site, which is the statistical methodology specified in the protocol and statistical analysis plan. My analyses that adjusted for baseline score and study were consistent with the findings from the analyses that adjusted for baseline only.

In keeping with the intent-to-treat principle, I recommend reporting results from the analyses of the MITT population (Table 6) and not the results from the per protocol analyses. The definitions used to define the per protocol population also defined the entry criteria for the study. The per protocol analyses can be considered to be sensitivity analyses. Their results are consistent with the finding from the ITT analyses.

5.2 Conclusions and Recommendations

The results support the efficacy of PVC 21/7 and PVC 2x/wk in their ability to reduce the severity of dyspareunia among healthy post-menopausal women with moderate-to-severe vaginal atrophy. These results were found both in the overall study population and in the sensitivity analyis of the per protocol population of women who had a baseline vaginal pH of 5 or greater, who had no more than 5 percent superficial cells on a vaginal smear and who reported a most bothersome symptom with a severity score of 2 or greater. Differences between treatment and placebo were not statistically significant for the other three symptoms: vaginal burning, vaginal dryness and vaginal itching.

In keeping with the intent-to-treat principle, I recommend reporting results from the analyses of the overall population (Table 6) and not the results from the per protocol analyses. The definitions used to select the per protocol population also defined the entry criteria for the study. The per protocol analyses can be considered to be sensitivity analyses. Their results are consistent with the finding from the ITT analyses.

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/s/

Lisa A. Kammerman
5/27/2008 12:19:52 PM
BIOMETRICS

Mahboob Sobhan
5/27/2008 01:38:54 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20216Orig1s060

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 20-216	Submission Date(s): September 5, 2008
Brand Name	Premarin Vaginal Cream
Generic Name	Conjugated estrogens
Reviewer	Doanh Tran, R.Ph., Ph.D.
OCP secondary reviewer	Hae Young Ahn, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Reproductive and Urologic Products
Sponsor	Wyeth
Submission Type	Class I resubmission to NDA 20-216/S-60
Formulation; Strength(s)	Cream, 0.625 mg conjugated estrogens per gram
Indication	Treatment of vulvar vaginal atrophy (VVA), dyspareunia associated with VVA or kraurosis vulvae

Recommendation:

This class I resubmission only contains a labeling proposal. The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds this resubmission to NDA 20-216 SE 060 acceptable, pending agreement with the Sponsor on labeling.

Summary of review:

Background:
Premarin vaginal cream (PVC) is a naturally derived product composed of a mixture of sodium estrone sulfate and sodium equilin sulfate that is blended to represent the average composition of material derived from pregnant mares' urine. It also contains concomitant components, as sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol, 17β-dihydroequilin.

PVC is indicated for the "treatment of atrophic vaginitis and kraurosis vulvae." The approved dose is cyclic administration of 0.5 to 2.0 g daily, intravaginally (i.e., three weeks on and one week off). In efficacy supplement 060, the sponsor sought an additional dosing schedule of 0.5 g twice weekly. The new schedule is based on the results of clinical study 0713S5-413-NA. Study 0713S5-413-NA evaluated the effect of 0.5 g PVC or placebo given under 2 dosing regimens, each 12 weeks in duration. In regimen 1, PVC or placebo was applied daily for 21 days followed by 7 days (b) (4) In regimen 2, PVC or placebo was applied 2 times a week every week. The sponsor also proposed to modify the indication to the following: "treatment of vulvar vaginal atrophy (VVA), dyspareunia associated with VVA or kraurosis vulvae."

No new pharmacokinetic data were submitted in this submission. The new dosing regimen represents a lower total dose compared to the approved dose. The currently approved drug product was used in protocol 0713S5-413-NA. Therefore, no PK bridging study was needed.

(b) (4)

(b) (4)

The Clinical Pharmacology review of sNDA 20-216 SE060 involved reformatting the Premarin Vaginal Cream label to comply with the Physician Labeling Rule. In addition, the PK information based on Dr. Sandra Suarez's review of data from study 0713S5-414-US was recommended to be added to the label.

The sNDA received an Approvable action on 7/25/2008 because labeling (unrelated to Clinical Pharmacology) remained unresolved.

Current submission:

In this resubmission, the sponsor has agreed to Clinical Pharmacology recommended labeling revisions sent to sponsor during the last review cycle. The main recommended revision was the addition of PK data for the Premarin Vaginal Cream group in study 0713S5-414-US. The recommendation included removal of PK comparisons to the oral Premarin tablet since the data are not needed for the use of Premarin Vaginal Cream and they may be misinterpreted to imply that the vaginal cream product may be safer than the oral product. It has not been shown that the lower relative systemic bioavailability of the vaginal cream product would correlate to lower safety adverse reactions.

However, one item was overlooked in the last review cycle. (b) (4)

(b) (4)

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/s/

Doanh Tran
10/6/2008 03:17:27 PM
BIOPHARMACEUTICS

Hae-Young Ahn
10/9/2008 11:17:17 AM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 20-216	Submission Date(s): September 25, 2007
Brand Name	Premarin Vaginal Cream
Generic Name	Conjugated estrogens
Reviewer	Doanh Tran, R.Ph., Ph.D.
Team Leader	Myong-Jin Kim, PharmD
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Reproductive and Urologic Products
Sponsor	Wyeth
Submission Type; Code	Efficacy supplement
Formulation; Strength(s)	Cream, 0.625 mg conjugated estrogens per gram
Indication	Treatment of vulvar vaginal atrophy (VVA), dyspareunia associated with VVA or kraurosis vulvae

Recommendation:

This efficacy supplement does not contain any new clinical pharmacology data. The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds supplemental NDA 20-216 SE 060 acceptable from a Clinical Pharmacology perspective, pending agreements with the Sponsor on labeling.

Summary of review:

Premarin vaginal cream (PVC) is a naturally derived product composed of a mixture of sodium estrone sulfate and sodium equilin sulfate that is blended to represent the average composition of material derived from pregnant mares' urine. It also contains concomitant components, as sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol, 17β-dihydroequilin.

PVC is indicated for the "treatment of atrophic vaginitis and kraurosis vulvae." The approved dose is cyclic administration of 0.5 to 2.0 g daily, intravaginally (i.e., three weeks on and one week off). In this efficacy supplement, the sponsor is seeking an additional dosing schedule of 0.5 g twice weekly. The new schedule is based on the results of clinical study 0713S5-413-NA. Study 0713S5-413-NA evaluated the effect of 0.5 g PVC or placebo given under 2 dosing regimens, each 12 weeks in duration. In regimen 1, PVC or placebo was applied daily for 21 days followed by 7 days without treatment. In regimen 2, PVC or placebo was applied 2 times a week every week. [redacted] (b) (4)

No new pharmacokinetic data were submitted in this submission. The new dosing regimen represents a lower total dose compared to the approved dose. The currently approved drug product was used in protocol 0713S5-413-NA. Therefore, no PK bridging study is needed.

[redacted] (b) (4)

(b) (4)

The Clinical Pharmacology review of the current sNDA involved reformatting the Premarin Vaginal Cream label to comply with the Physician Labeling Rule. In addition, negotiation with sponsor to add the PK information based on Dr. Sandra Suarez's review of data from study 0713S5-414-US will take place.

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/s/

Doanh Tran
5/16/2008 04:34:08 PM
BIOPHARMACEUTICS

Myong-Jin Kim
5/19/2008 01:01:22 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20216Orig1s060

OTHER REVIEW(S)

Medical Officer's Review of sNDA 20-216/SE1-060 Labeling

TO:	sNDA 20-216/SE1-060
FROM:	Theresa H. van der Vlugt, MD, M.P.H. Medical Officer Division of Reproductive and Urologic Products
THROUGH:	Shelley Slaughter. MD, Ph.D. Medical Team Leader Division of Reproductive and Urologic Products
SUBJECT:	Response to Approvable Letter dated July 25, 2008: Class I Resubmission
DATE:	November 6, 2008

Background:

sNDA 20-216/SE1-060 was submitted by Wyeth Pharmaceuticals, Inc. on September 25, 2007 for a treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause indication. On July 25, 2008, Wyeth Pharmaceuticals, Inc. received an Approvable letter from the Agency indicating the following:

"We have completed our review of this application, as amended, and it is approvable because labeling remains unresolved. Because we have failed to come to agreement on the labeling, including the indication section, we will continue discussions based on the version we sent to you on July 2, 2008. If additional information relating to the safety or effectiveness of this drug becomes available, additional revision of the labeling may be required."

On September 5, 2008, Wyeth Pharmaceuticals, Inc. submitted a "Response to Approvable Letter dated July 25, 2008; Class I Resubmission." The proposed PLR formatted PREMARIN® Vaginal Cream (PVC) labeling in the resubmission included changes such as:

(b) (4)

The proposed PREMARIN® Vaginal Cream labeling submitted on September 5, 2008 was reviewed it its entirety. In the September 5, 2008 labeling submitted, Wyeth

Pharmaceutical, Inc. indicates both their agreement with and their disagreement with the Agency's revised labeling sent on July 2, 2008.

Labeling Actions:

On October 29, 2008, the Division of Reproductive and Urologic Products (DRUP) provided Wyeth Pharmaceuticals, Inc. with recommended changes to the PREMARIN® Vaginal Cream labeling submitted on September 5, 2008. On October 31, 2008, Wyeth Pharmaceuticals, Inc. submitted revised labeling to DRUP.

The Division completed a teleconference with Wyeth on October 31, 2008. In this teleconference the Division and Wyeth reached agreement on the:

- Black box warning (headings, subheadings, and content) in the Highlights and Full Prescribing Information sections of labeling.
- Retention of the following statements in both boxed warnings (Highlights and Full Prescribing Information sections), (b) (4)
- Retention of the following statement in the Full Prescribing Information boxed warning. (b) (4)
- (b) (4)
- (b) (4)
- Retention of the 95 percent confidence intervals in relative risk statements in labeling text when this information is not available in tables.
- Revision and reformatting of Table 3.
- Revision of the applicable references and footnotes in Table 5.
- Retention of the first indication bullet in the PATIENT INFORMATION leaflet, (b) (4)

In this teleconference, however, the Division and Wyeth did not reach agreement on subsection 6.2 Postmarketing Experience in the Full Prescribing Information section of labeling. (b) (4)

The Division also requested on October 31, 2008 that the following modifications be made to the PREMARIN® Vaginal Cream carton and tube:

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]

Wyeth Pharmaceuticals, Inc. submitted final mock ups of the PREMARIN Vaginal Cream carton and the tube label on November 3, 2008 and November 4, 2008, respectively. All requested changes were evident.

On November 2, 2008, Wyeth Pharmaceuticals, Inc. submitted a second revised label for PREMARIN Vaginal Cream. This labeling contained all of the information the Division and Wyeth agreed upon during the October 31, 2008 teleconference. Subsection 6.2 Postmarketing Experience, and its content, remained unresolved, however.

The Division completed a second teleconference with Wyeth Pharmaceuticals, Inc. on November 3, 2008. The Division and Wyeth reached agreement during this teleconference on the:

1. Wording of the Highlights section of labeling under "Indication and Usage" as follows:

[redacted]

2. Wording of the Highlights section of labeling under "Dosage and Administration" as follows:

- [redacted]

3. [redacted] (b) (4)

Wyeth Pharmaceuticals, Inc. indicated during the November 3, 2008 teleconference their willingness to include adverse reactions reported with PREMARIN® Vaginal Cream in subsection 6.2 Postmarketing Experiences.

Revised labeling was provided by Wyeth Pharmaceuticals, Inc. on November 4, 2008. All agreed upon revisions to labeling were included except for subsection 6.2 Postmarketing Experience, which Wyeth indicated was still under revision.

On November 5, 2008, the Division requested that the following additional modification be made to the PREMARIN® Vaginal Cream carton:

1. [redacted] (b) (4)

Wyeth Pharmaceuticals, Inc. submitted a final mock up of the PREMARIN® Vaginal Cream carton on November 6, 2005 with the statement deleted.

A "final" PREMARIN® Vaginal Cream label was submitted by Wyeth on November 5, 2008. It was noted that subsection 6.2 Postmarketing Experience was updated. However, the Division disagreed with the wording of the first sentence in the first paragraph which did not reflect prior agreed upon language. Wyeth was informed by teleconference of the Division's concerns. Wyeth agreed that the sentence in question did not express the agreed upon language, and indicated that a "final" PREMARIN® Vaginal Cream label would be provided on November 6, 2008. In addition, a few minor editorial revisions were required, and these were also communicated to Wyeth.

On November 6, 2006, DRUP and Wyeth Pharmaceuticals, Inc. reached an agreement on the final PREMARIN Vaginal Cream labeling in a PLR format.

Recommendations and Comments:

The reviewer recommends the approval of the final agreed upon PREMARIN® Vaginal Cream labeling attached to this review. Wyeth Pharmaceutical, Inc. should be advised in a regulatory letter of the approval of sNDA 20-216/SE1-060.

ATTACHMENT:

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/s/

Theresa Van Der Vlugt
11/6/2008 05:44:40 PM
MEDICAL OFFICER

Shelley Slaughter
11/6/2008 07:37:39 PM
MEDICAL OFFICER
I concur with Dr. van der Vlugt's summary and timelines of the succesful labeling negotiations with Wyeth Pharmaceuticals, Inc. I concur in the recommendation that this labeling for SE1 060 be approved.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 30, 2008
To:	Scott Monroe, M.D., Director Division of Reproductive & Urologic Products
Through:	Jodi Duckhorn, M.A. Team Leader Patient Labeling and Education Team Division of Risk Management
From:	Nancy Carothers Patient Product Information Specialist Patient Labeling and Education Team Division of Risk Management
Subject:	Review of Patient Labeling for a low dose regimen
Drug Name(s):	Premarin Cream® (0.625 mg. conjugated estrogen)
Application Type/Number:	NDA 20-216/S-060
Applicant/sponsor:	Wyeth Pharmaceuticals, Inc.
OSE RCM #:	2008-781

INTRODUCTION

Premarin Cream® is an estrogen product indicated for moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. (b) (4) [redacted] Premarin Cream was first approved for atrophic vaginitis and kaurosis vulvae on October 16, 1978.

The FDA encouraged the development of the lowest doses and exposures for estrogens and progestins, and the sponsor has developed a lower dose regimen of this product. The proposed labeling for the low dose treatment was submitted on September 25, 2007 as Supplement #060. On January 25, 2008, the sponsor submitted an amendment to supplement #060 by providing a 4 Month Safety Update in support of Protocol 0713S5-413-NA. This refers to endometrial safety data.

The Division of Reproductive and Urologic Products requested that the Patient Labeling and Education Team review the Patient Package Insert (PPI) for the low dose regimen. On May 8, 2008, the sponsor proposed a name change for this product from Premarin Vaginal Cream to Premarin Cream.

MATERIAL rEVIEWED

- Premarin Cream® PI submitted by the Sponsor on May 8, 2008
- Premarin Cream® PPI submitted by the Sponsor on May 8, 2008

DISCUSSION

The purpose of the PPI is to enhance appropriate use of and to provide important risk information about medicines. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.
In our review we have:

- simplified the wording where possible,
- made the information in the PPI consistent with the PI,
- removed unnecessary and redundant information in the PPI,
- assessed the Patient Instructions for Use,
- ensured that the PPI is consistent with the November 2005 (Revision 4) *Draft Guidance for Industry: Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Prescribing Information for health Care Providers and Patient Labeling*, based on the WHI study.

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI. Comments to the review division are ***bolded, underlined, and italicized***.

We are providing to the review division a marked-up and clean copy of the revised PPI.

CONCLUSIONS AND RECOMMENDATIONS

(b)(4)

Please let us know if you have any questions.

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/s/

Nancy B Carothers
6/30/2008 05:45:14 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
7/1/2008 08:49:03 AM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: May 9, 2008

TO: George Lyght, Regulatory Project Manager
Theresa Van Der Vlugt, M.D., Medical Officer
Division of Reproductive and Urologic Products (DRUP)

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Jose Javier Tavarez, M.S.
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 20-216/060

APPLICANT: Wyeth Pharmaceuticals, Inc.

DRUG: Premarin® Vaginal Cream (PVC)(conjugated estrogens)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of vulvar vaginal atrophy or kraurosis vulvae

CONSULTATION REQUEST DATE: January 8, 2008

DIVISION ACTION GOAL DATE: June 1, 2008

PDUFA DATE: July 25, 2008

I. BACKGROUND

Clinical investigator inspections were requested at two clinical sites that performed studies for which the sponsor submitted data in NDA 20-216/060. The clinical investigator inspections were conducted according to the Compliance Program 7348.811, the Inspection Program for Clinical Investigators. The inspections covered work performed under protocol 0713S5-413-NA entitled "Efficacy and Safety of Two Low-Dose Regimens of Conjugated Estrogens Cream Administered Vaginally in Postmenopausal Women With Atrophic Vaginitis."

In this NDA, the sponsor has included results of protocol 0713S5-413-NA. Study protocol 0713S5-413-NA was a multicenter, double-blind, randomized, placebo-controlled, phase 3b trial, which was conducted at 49 sites in Canada and the United States. This study evaluated the efficacy and safety of a low-dose (0.3 mg) of PVC (0.625 mg/g) administered by 1 of 2 dose regimens for 12 weeks: the labeled regimen (once daily for 21 days, off for 7 days [PVC-21/7]) and an intermittent regimen (twice weekly [PVC-2x/wk]) that follows current prescribing practice. Each regimen was compared with its corresponding placebo group.

Basis for Site Selection: Two clinical sites (Drs. Lubin and Bouchard) were inspected. These sites were selected for inspection due to significant primary efficacy results pertinent to decision-making. The goals of inspection included validation of submitted data and compliance of study activities with FDA regulations. Among the elements reviewed for compliance were subject record accuracy, informed consent, protocol inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of adverse events.

II. RESULTS (by site):

Clinical Investigator/Site	Protocol(s)/# of subjects	Inspection Date	Final Classification
Dr. Barry Lubin Hampton Rhodes Center for Clinical Research 885 Kempsville Rd. Suite221 Norfolk, VA 23502	0713S5-413-NA 15 subjects	2/25 - 3/10/2008	VAI
Dr. Celine Bouchard Clinique RSF Inc. Center Medical Berger 1000, chemin Sainte-Foy Bureau 102 Quebec, Canada G1S 2L6	0713S5-413-NA 36 subjects	3/3-6/2008	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Dr. Barry Lubin
Norfolk, VA

a. What was inspected?

A total of 21 subjects were screened and 15 were randomized into the study; 11 completed the study and 4 discontinued: 1) one subject withdrew due to personal reasons and 2) three subjects had adverse events (one developed vaginal burning, one complained of multiple pains, headache, and one developed vaginal/vulva rash, possible allergy to carrier gel). The FDA investigator performed a complete review of all 15 subject's files.

The inspection was conducted according to the Compliance Program 7348.811, the Inspection Program for Clinical Investigators. The goals of inspection included validation of submitted data and compliance of study activities with federal regulations. Complete files were reviewed for all subjects including study regulatory records, case report forms (CRFs), and other study-specific source documents filed with the CRFs. Records were reviewed for informed consent, IRB approval, drug accountability, diagnosis, and entry criteria. Source documents were compared with data listings provided in the NDA for verification of safety and efficacy endpoints. The inspection encompassed an audit of all subjects' consent forms.

b. General observations/commentary:

In general, Dr. Lubin complied with protocol specified requirements; however, there was an instance where the inspection documented that Dr. Lubin was in noncompliance with the regulations, specifically: failure to conduct the study in accordance with the approved protocol [21 CFR 312.60]. Subject (b) (6) did not meet the protocol entry criterion requiring a vaginal maturation index (VMI) score of ≤ 5% superficial cells as determined from a vaginal cytological smear.

There were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events was noted. Data in sponsor-provided data listings were supported by data in source documents and case report forms.

c. Assessment of data integrity:

The review division may wish to exclude from efficacy analyses the subject who failed the study eligibility criterion as stated above. Overall, data generated for protocol 0713S5-413-NA at this clinical site appear acceptable for use in support of NDA 20-216/060.

2. Dr. Celine Bouchard
Quebec, Canada

a. What was inspected?

The FDA investigator reviewed the study records for all 36 subjects enrolled in the study. The FDA investigator reviewed the source documents and case report forms (CRFs), and compared these with data listings provided by the sponsor as part of the NDA submission. Among the elements reviewed for compliance were subject record accuracy, informed consent, protocol inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of adverse events. The inspection encompassed an audit of all subjects' consent forms.

b. General observations/commentary:

There were no significant inspectional findings that would adversely impact data acceptability. There was adequate documentation in the source documents to assure all subjects were actually enrolled in the study and treated throughout the study. No underreporting of adverse events was noted. Data in sponsor-provided data listings, including efficacy and safety endpoints, were supported by data in source documents and case report forms.

c. Assessment of data integrity:

Data generated for protocol 0713S5-413-NA at this clinical site appear acceptable for use in support of NDA 20-216/060 .

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As stated above, there was an instance of protocol deviation at Dr. Lubin's site. In general, for the two clinical investigator sites inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol.

No underreporting of adverse events was noted. Overall, data generated for protocol 0713S5-413-NA at these clinical sites appear acceptable for use in support of NDA 20-216/060.

{See appended electronic signature page}

Jose Javier Tavarez, M.S.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Jose Tavarezpagan
5/15/2008 10:18:49 AM
CSO

Constance Lewin
5/15/2008 10:20:48 AM
MEDICAL OFFICER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 21, 2008
To:	Scott Monroe, M.D., Director Division of Reproductive and Urologic Products
Thru:	Todd Bridges, RPh, Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention
From:	Diane C. Smith, PharmD, Safety Evaluator Division of Medication Error Prevention
Subject:	Labeling Review for Premarin Vaginal Cream
Drug Name(s):	Premarin (Conjugated Estrogens) Vaginal Cream
Application Type/Number:	NDA 20-216
Applicant/sponsor:	Wyeth Pharmaceuticals Inc.
OSE RCM #:	2008-153

CONTENTS

EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment for Premarin Vaginal Cream found that the graphic and banner on carton labeling distracts attention away from important information such as the proprietary and established names . (b) (4) [redacted] We believe the risks we have identified can be addressed and mitigated prior to approval and we have provided recommendations in Section 5 of this review.

1 BACKGROUND

1.1 INTRODUCTION

This memorandum is in response to a January 16, 2008, request from the Division of Urologic and Reproductive Products for a review of the container labels, carton and insert labeling of Premarin Vaginal Cream.

1.2 REGULATORY HISTORY

Premarin Vaginal Cream, marketed by Wyeth Pharmaceuticals Inc., was approved by FDA on October 16, 1978, for the treatment of atrophic vaginitis and kraurosis vulvae. On September 25, 2007, the applicant submitted an efficacy supplement for a new low dose of 0.5 gm twice weekly. The container labels and carton and insert labeling were submitted for review.

1.3 PRODUCT INFORMATION

Premarin Vaginal Cream (conjugated estrogens) contains 0.625 mg of conjugated estrogens, in a nonliquefying base. The cream is applied intravaginally. Premarin Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. Premarin Vaginal Cream is currently dosed 0.5 to 2 g daily, whereas the proposed alternate low dose will be 0.5 g twice weekly.

2 METHODS AND MATERIALS

2.1 AERS SELECTION OF CASES

Since Premarin Vaginal Cream is already marketed, the Division of Medication Error Prevention searched the FDA Adverse Events Reporting System (AERS) using the trade name "Premar%", and the verbatim entry "Premar %" with MedDRA High Level Group Term "Medication Error" and the Preferred Term "Pharmaceutical Product Complaint" to identify problems, if any, with this product line.

2.2 PROPOSED LABEL/LABELING

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[1]

Because the Division of Medication Error staff analyzes reported misuse of drugs, the medication error staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. The Division of Medication Error Prevention uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

For this product, the sponsor submitted on September 25, 2007, the following labels and labeling for our review (see Appendix A):

- Carton Labeling
- Container Label
- Prescribing Information- package insert (no image)

3 RESULTS

3.1 AERS SELECTION OF CASES

This search did not retrieve any cases of postmarketing confusion with the nomenclature for the product line or the Premarin Vaginal Cream labels or labeling.

3.2 LABEL AND LABELING RISK ASSESSMENT

Review of the container label and carton labeling identified several potential sources of medication errors. These concerns are noted below.

3.2.1 Container Label and Carton Labeling

3.2.2 Insert/Patient Insert labeling

We have no comments on the package insert at this time.

[1] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p. 275.

4 DISCUSSION

Our analysis of the container labels and carton labeling noted areas of vulnerability that could lead to medication errors. [redacted] (b) (4)

[redacted] Relocating this statement to a less prominent location will allow the health care practitioner to focus on the important information such as the proprietary and established names, and dosage form.

[redacted] (b) (4)

[redacted] Both of these statements are more prominent than the proprietary and established names. Thus, these yellow highlighted statements distract from important information such as the proprietary and established name.

5 CONCLUSIONS AND RECOMMENDATIONS

The Division of Medication Error Prevention recommends that the label and labeling recommendations outlined in section 5.2 below be implemented to improve the overall presentation of information on the container label and carton labeling.

5.1 COMMENTS TO THE DIVISION

Based upon our Label and Labeling Risk Assessment, we have identified areas of needed improvement. We believe the risks we have identified can be addressed and mitigated prior to approval and we have provided recommendations in Section 5.2 and request that this information be forwarded to the Applicant.

The Division of Medication Error Prevention would appreciate feedback on the final outcome of this review. Please copy the Division of Medication Error Prevention on any communication to the Applicant with regard to this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Cherye Milburn, Project Manager, at 301-796-2084.

5.2 COMMENTS TO THE SPONSOR

[redacted] (b) (4)

[redacted] (b) (4)

6 APPENDIX

Container Label and Carton Labeling for Premarin Vaginal Cream

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/s/

Diane Smith
3/21/2008 04:33:36 PM
CSO

Todd Bridges
3/21/2008 04:37:40 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
3/21/2008 04:53:04 PM
DRUG SAFETY OFFICE REVIEWER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	03/12/2008
To:	Scott Monroe, M.D., Director Division of Reproductive and Urologic Products
From:	Adrienne M. Rothstein, Pharm.D., Safety Evaluator Division of Adverse Event Analysis II
	David Moeny, R.Ph. CDR, USPHS Drug Utilization Data Analyst Division of Epidemiology
Through	Melissa M. Truffa, R.Ph., Safety Evaluator Team Leader Division of Adverse Event Analysis II
Through:	Ann W. McMahon, M.D., M.S., Acting Director, Division of Adverse Event Analysis II
Subject:	Safety Review of Premarin Vaginal Cream New Efficacy Supplement
Drug Name(s):	Premarin Vaginal Cream (conjugated estrogens)
Submission Number:	S-060
Application Type/Number:	20-216
Applicant/sponsor:	Wyeth Pharmaceuticals
OSE RCM #:	2007-2355

CONTENTS

EXECUTIVE SUMMARY

Division of Drug Risk Evaluation (DDRE) was consulted for a safety review for Premarin Vaginal Cream (conjugated estrogens) related to an efficacy supplement (S-060) for a new dosing regimen of 0.5 gram intravaginally twice weekly, which is a lower strength than currently approved dosage regimens. A recent draft guidance from the FDA encourages sponsors to develop the lowest doses and exposures for both estrogens and progestins for indications sought, even though specific relationships between dose, exposure, and risk of adverse events may not be known.

For the data mining analysis MedDRA preferred terms with EB05 $\geq$ 2 scores were reviewed. The AERS database was also searched for reports for Premarin Vaginal cream or Premarin administered by relevant routes of administration. The preferred terms with the highest data mining scores and the most commonly reported preferred terms in AERS were reviewed and compared against the current labeling for Premarin Vaginal Cream. This review did not identify any new or unexpected adverse event terms for consideration as additions to the proposed labeling.

1 BACKGROUND

1.1 INTRODUCTION

DDRE was consulted for a safety review for Premarin Vaginal Cream (conjugated estrogens) related to a September 25, 2007 efficacy supplement (S-060) for a new dosing regimen of 0.5 gram intravaginally twice weekly. The approved dosages range from 0.5 to 2 grams applied intravaginally daily for cycles of three weeks on, then one week off. The indication for use for this product is the treatment of vulvar vaginal atrophy (VVA), dyspareunia associated with VVA or kraurosis vulvae.

This safety review will examine the most commonly reported adverse event terms in the AERS database, significant data mining scores and will provide the most current drug usage information. This product has not been previously reviewed by the Office of Surveillance and Epidemiology.

1.2 REGULATORY HISTORY

In a Federal Register notice (DESI 2238; Docket no. FDC-D500 [now Docket No. 76N-0261]) published in July 27, 1972 (37 FR 15028), the FDA announced that Premarin Vaginal Cream was effective in the treatment of atrophic vaginitis and kraurosis vulvae. Ayerst Laboratories, a Division of the American Home Products Corp., now Wyeth Pharmaceuticals Inc., received approval for ANDA 83-273 on October 16, 1978 for Premarin Vaginal Cream (0.625 mg of conjugated estrogens, USP per gram of cream).
In January 2003, the FDA published a draft guidance "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation." This guidance encourages sponsors to develop the lowest doses and exposures for both estrogens and progestins for indications sought, even though specific relationships between dose, exposure, and risk of adverse events may not be known. Sponsors are encouraged to investigate dosing schedules and drug delivery systems that can achieve efficacy with lowest possible exposures.

On September 25, 2007, the sponsor submitted an efficacy supplement for a new dosing regimen of 0.5 grams intravaginally twice weekly for the treatment of vulvar vaginal atrophy (VVA), dyspareunia associated with VVA or kraurosis vulvae.

1.3 PRODUCT LABELING

The proposed product labeling is available via the link provided in Appendix 1.

2 METHODS AND MATERIALS

2.1 DATA MINING

The term 'data mining' refers to the use of computerized algorithms to discover hidden patterns of associations or unexpected occurrences (i.e. 'signals') in large databases. These signals can then be evaluated for intervention as appropriate.

The Bayesian algorithm used for the data mining analysis was the Multi-Item Gamma Poisson Shrinker (MGPS).[1, 2] This algorithm analyzes the records contained in large post-marketing drug safety databases and then quantifies potential drug-event associations by producing a ranked set of values or scores which indicate varying strengths of reporting relationships between drugs and events. The **EB05** is an estimated lower 95% "confidence limit" for the adjusted observed-to-expected (N/E) ratio calculated by the data mining algorithm. EB05 is useful for ensuring with high probability that the observed-to-expected ratio for a particular item set (e.g., drug-event combination) *exceeds* a certain value. Thus, using an EB05 ≥ 2 as a signal definition indicates 95% confidence that a drug-event combination in question occurs at least at twice the expected rate when considering all other drugs and events in the database.

Search Strategy:

The WebVDME data mining application from Lincoln Technologies was searched on 1/14/08 using the trade name "Premarin." All preferred terms (PTs) with an EB05 ≥ 2.0 were retrieved (these reports were not reviewed individually).

2.2 AERS SELECTION OF CASES

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. FDA receives adverse drug reaction reports from manufacturers as required by regulation, including both foreign and domestic reports. Health care professionals and consumers send reports voluntarily through the MedWatch program. Based on data entry rules, the adverse event reports are entered into the AERS database. All reported adverse event terms are coded using a standardized international terminology, MedDRA (the Medical Dictionary for Regulatory Activities).

Search Strategy:

The AERS database was searched as follows:

- Any report with the suspect drug Premarin Vaginal Cream listed as the Trade Name (search date 1/14/08)
- Any report with the suspect drug Premarin listed as the Trade Name with the following routes of administration noted: vaginal, topical, cutaneous, endocervical (search date 1/15/08)

[1] DuMouchel W, Pregibon D. Empirical bayes screening for multi-item associations. Proceedings of the conference on knowledge discovery and data; 2001 Aug 26-29; San Diego (CA): ACM Press: 67-76.
[2] Szarfman A, Machado SG, O'Neill RT. Use of Screening Algorithms and Computer Systems to Efficiently Signal Higher-Than-Expected Combinations of Drugs and Events in the US FDA's Spontaneous Reports Database. Drug Safety 2002; 25:381-392.

Due to the volume of reports for this medication, no attempt was made to eliminate duplicates or reports retrieved inadvertently. For example, reports were retrieved if they contained Premarin and *any* suspect drug administered by the vaginal, topical, cutaneous, or endocervical route. These reports were not removed from the search results. In addition, many reports were retrieved that noted that the patient was receiving both oral Premarin and Premarin Vaginal Cream. These reports were not removed from the search results.

2.3 OTHER DATABASES

IMS Health, IMS National Sales Perspectives™ data were used to determine the primary settings in which conjugated estrogens vaginal cream is sold. Cumulative sales of these products by number of tubes of product sole sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for the years 2003 through 2007. A complete description of this IMS Health database is provided in Appendix One.

(b) (4)

Because most of the product sold during this time period went to retail pharmacies, we examined utilization patterns focusing on the outpatient setting. Sales data indicate that the Verispan retail pharmacy prescription databases are the most appropriate data sources to measure the use of these products among the databases licensed by FDA.

2.4 DATA SOURCES USED

Outpatient use and patient demographics were measured with two data sources from Verispan, LLC: Vector One®: National (VONA), and Total Patient Tracker (TPT). From these sources, nationally projected estimates of the number of prescriptions dispensed by retail pharmacies and the number of patients who received a prescription dispensed by retail pharmacies for carvedilol were obtained. Outpatient drug utilization patterns were examined for the five calendar years from 2003 through 2007.

3 RESULTS

3.1 DATA MINING

All preferred terms (N = 85) with an EB05 score ≥ 2.0 are presented in **Table 1**. The highest data mining scores and the most commonly reported preferred terms were related to breast cancer. Of the 40 highest data mining scores, 30 preferred terms were related to breast cancer or its diagnosis and treatment. Other preferred terms with high data mining scores relate to endometrial cancer, ovarian cancer and thromboembolic events.

(b) (4)

[3] (b) (4)

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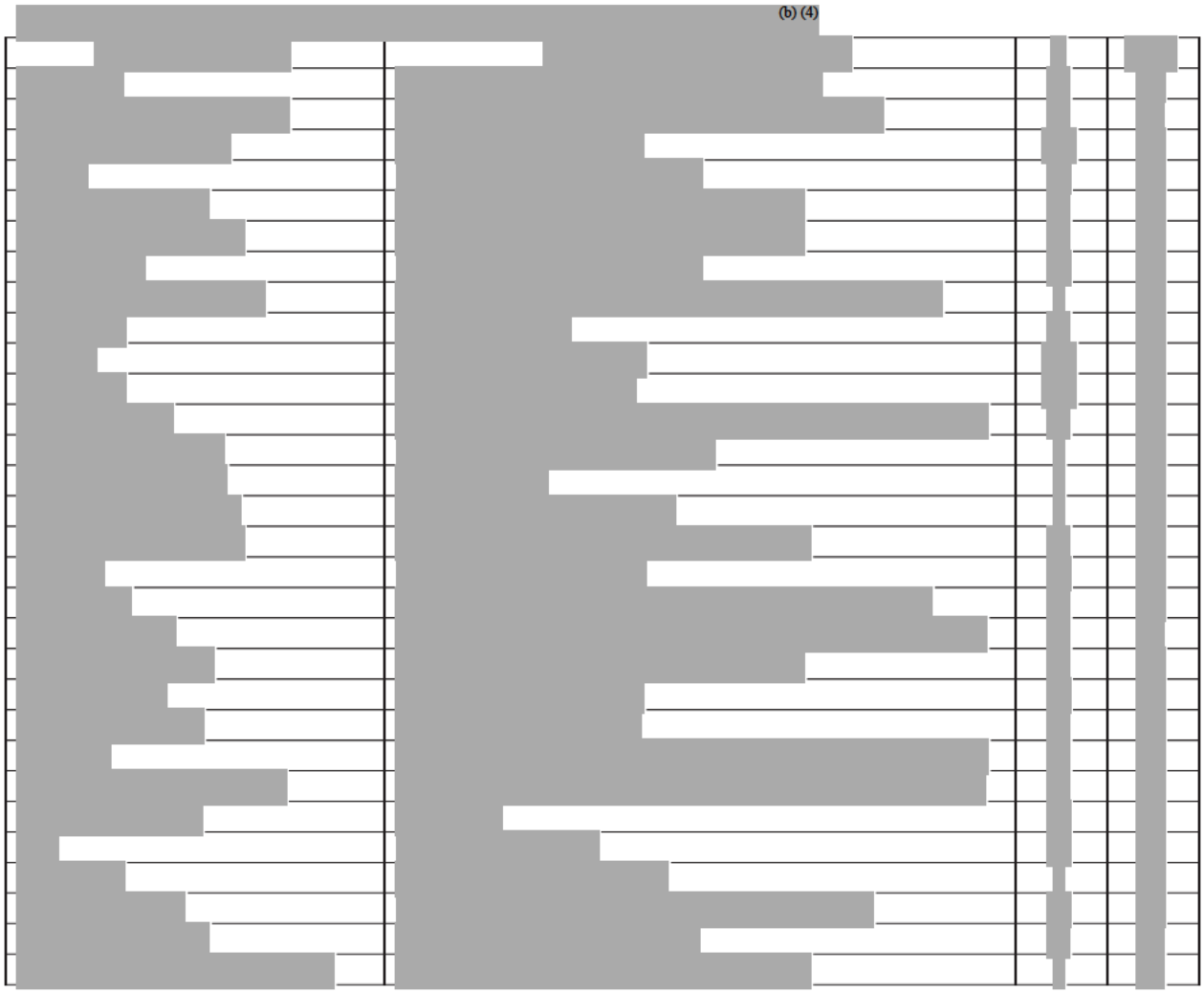

3.2 ADVERSE EVENT CASES

A search of the AERS database for any report with the suspect drug Premarin Vaginal Cream listed as the Trade Name retrieved 49 cases in AERS. The most commonly reported PTs are listed in **Table 2** below.

The events listed in **Table 2** were compared against the current labeling and symptoms associated with the indication for use. The FDA draft guidance for the clinical evaluation of "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms" was consulted for symptoms associated with the indication for use in this patient population. The symptoms of vulvar and vaginal atrophy include: vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, vaginal pain associated with sexual activity, and vaginal bleeding associated with sexual activity. Vasomotor symptoms in postmenopausal women are commonly known as hot flushes or hot flashes and describe a sensation of heat with or without sweating. The only events listed in **Table 2** that are not labeled or confounded by the indication for use are abdominal pain, drug ineffective, pain, and urinary tract infection. The number of reports retrieved was too limited to draw any further conclusions.

Table 2. Most Commonly Reported PTs for Premarin Vaginal Cream (Trade Name) (N = 49 AERS cases)

Preferred Term (PT)	Count of PTs	% of Total
Vaginal Infection	6	12.24
Breast Pain	4	8.16
Pruritus	4	8.16
Abdominal Pain	3	6.12
Alopecia	3	6.12
Breast Cancer Female	3	6.12
Dermatitis	3	6.12
Drug Ineffective	3	6.12
Pain	3	6.12
Vaginal Discharge	3	6.12
Hyperhidrosis	2	4.08
Nausea	2	4.08
Pruritus Genital	2	4.08
Urinary Tract Infection	2	4.08
Vaginal Candidiasis	2	4.08
Vaginal Haemorrhage	2	4.08
Vaginal Pain	2	4.08

A search of the AERS database for any report with the suspect drug Premarin (Trade Name) and the queried route of administration (vaginal, topical, cutaneous, endocervical) retrieved 926 cases.

The most commonly reported PTs in these 926 cases are listed below in **Table 3**. These events were compared against the current labeling and symptoms associated with the indication for use. The only events listed in **Table 3** that are not labeled or confounded by the indication for use are pain, drug ineffective, abdominal pain, condition aggravated, dyspnea, back pain, unevaluable event, urinary tract infection, asthenia, paresthesia, pelvic pain, abdominal distension, flatulence, and osteoarthritis.

Table 3. Most Commonly Reported PTs for Premarin (Trade Name) With Administration Routes of Vaginal, Topical, Cutaneous, or Endocervical (N = 926 AERS cases)

Preferred Term (PT)	Count of PTs	% of Total
Vaginal Infection	196	21.17
Application Site Reaction	92	9.94
Pain	57	6.16
Drug Ineffective	56	6.05
Breast Pain	52	5.62
Pruritus	52	5.62
Abdominal Pain	44	4.75
Dermatitis	41	4.43
Headache	41	4.43
Breast Cancer	36	3.89
Alopecia	34	3.67
Condition Aggravated	33	3.56
Dizziness	32	3.46
Hypersensitivity	26	2.81
Nausea	26	2.81
Vaginal Candidiasis	26	2.81
Depression	25	2.7
Vaginal Haemorrhage	22	2.38
Vaginal Discharge	21	2.27
Breast Enlargement	18	1.94

Table 3. Most Commonly Reported PTs for Premarin (Trade Name) With Administration Routes of Vaginal, Topical, Cutaneous, or Endocervical (N = 926 AERS cases)

Preferred Term (PT)	Count of PTs	% of Total
Cystitis	18	1.94
Menometrorrhagia	18	1.94
Vulvovaginitis	18	1.94
Dyspnoea	17	1.84
Oedema	17	1.84
Vaginal Pain	15	1.62
Weight Increased	15	1.62
Arthralgia	14	1.51
Back Pain	12	1.3
Unevaluable Event	12	1.3
Urinary Tract Infection	12	1.3
Asthenia	11	1.19
Breast Cancer Female	11	1.19
Dysuria	11	1.19
Hypertension	11	1.19
Oedema Peripheral	11	1.19
Pain In Extremity	11	1.19
Paraesthesia	11	1.19
Pelvic Pain	11	1.19
Abdominal Distension	10	1.08
Flatulence	10	1.08
Hirsutism	10	1.08
Osteoarthritis	10	1.08

3.3 Drug Utilization Data

3.3.1 Retail Prescriptions

The projected number of conjugated estrogens vaginal cream prescriptions dispensed in the U.S. by retail pharmacies was obtained using Verispan's Vector One: National (Appendix 2, Table 1).

(b) (4)

(b) (4)

3.3.2 Retail Patient Counts

The projected number of patients receiving a conjugated estrogens vaginal cream prescription dispensed through a U.S. retail pharmacy was obtained using Verispan's Total Patient Tracker (Appendix 2, Table 2). The trends seen in the patient count data were similar to those observed in the prescription data.

(b) (4)

4 DISCUSSION

4.1 DATA MINING

For the Data Mining analysis, MedDRA preferred terms with an EB05 score ≥ 2.0 for the trade name Premarin were retrieved (see **Table 1)**. These preferred terms were then compared against the adverse event terms listed in the current prescribing information. The preferred terms with the highest data mining scores and the most commonly reported preferred terms as presented in **Table 1** relate to breast cancer. Other preferred terms with high data mining scores relate to endometrial cancer, ovarian cancer and thromboembolic events. As mentioned previously, many of these reports mentioned use of Premarin Vaginal Cream and Premarin oral tablets, among other therapies. It is not known how many reports only involved Premarin Vaginal Cream. Due to the volume of reports, a hands-on review was not feasible.

As noted in the current labeling for Premarin Vaginal Cream and Premarin oral tablets, there is a **BOXED WARNING** that estrogens increase the risk of endometrial cancer, stroke, and deep vein thrombosis based on data from the Women's Health Initiative study. The **BOXED WARNING** also warns that estrogen-plus-progestin increased the risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and deep vein thrombosis in post-menopausal women receiving *oral* conjugated estrogens with medroxyprogesterone acetate. These **BOXED WARNINGS** follow the recommendations in the draft guidance for industry "Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms - Recommended Prescribing Information for Health Care Providers and Patient Labeling" (dated November 2005).

Thus, data mining did not identify any new or unexpected adverse event terms for consideration as additions to the proposed labeling.

4.2 ADVERSE EVENT CASES

The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Hence, when considering counts of cases generated from AERS, it should be realized that case reports cannot be used to calculate incidence or estimates of drug risk for a particular product, as reporting of adverse events is a voluntary process, and underreporting exists. Further, because of the multiple factors, which influence reporting, comparisons of drug safety cannot be made from these data. Some of these factors include the length of time a drug is marketed, the market share, size and sophistication of the sales force, publicity about an adverse reaction and regulatory actions (e.g. Women's Health Initiative study results).

It should also be noted that in some reported cases, the clinical data are incomplete, and there is no certainty that these drugs caused the reported reactions. A given reaction may actually have been due to an underlying disease process or to another coincidental factor. Further, these data often contain duplicates and manual review is required to distinguish unique patients. As mentioned previously, many of these reports note use of Premarin Vaginal Cream and Premarin oral tablets. In addition, many reports retrieved involved *oral* Premarin plus another suspect drug administered by the routes of administration queried. Due to the volume of reports, a manual review was not feasible to determine the exact numbers for these observations. Instead, the AERS database was searched using two sets of search criteria and data mining scores were retrieved. For both, commonly reported preferred terms were compared against the current labeling to identify new or unexpected adverse event terms. This review of post-marketing data did not attempt to determine if there were reports of lack of efficacy with the currently marketed Premarin Vaginal Cream product. The efficacy data for Premarin Vaginal Cream is best obtained

from randomized, controlled clinical trials, which the sponsor has provided to support the lower dosing regimen.

A search of the AERS database for any report with the suspect drug Premarin Vaginal Cream listed as the Trade Name retrieved 49 cases in AERS. The most commonly reported unlabeled PTs in this limited case series were abdominal pain, drug ineffective, pain, and urinary tract infection. There were too few reports retrieved using this search strategy to draw any further conclusions.

A second search of the AERS database for any report with the suspect drug Premarin (Trade Name) with vaginal, topical, cutaneous, or endocervical routes of administration retrieved 926 cases. For the second AERS search, the most commonly reported unlabeled PTs were pain, drug ineffective, abdominal pain, condition aggravated, dyspnea, back pain, unevaluable event, urinary tract infection, asthenia, paresthesia, pelvic pain, abdominal distension, flatulence, and osteoarthritis.

Many of these adverse event terms retrieved from both searches were too non-specific to be meaningful (e.g., pain, condition aggravated, drug ineffective) or represent diseases or conditions common in the population using the product (e.g. osteoarthritis, urinary tract infection). Thus, the searches of the AERS database did not identify any new or unexpected adverse event terms for consideration as additions to the proposed labeling.

4.3 DRUG UTILIZATION DATA

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that the use of this product was primarily in the outpatient settings based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of the number of tablets sold from the manufacturer to various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use. The actual proportion of overall prescription dispensing by each pharmacy channel will differ based on the average prescription size dispensed.

While we conducted a comprehensive analysis of the use of this product in the outpatient settings in which the majority of use occurred, use outside of the retail pharmacy setting was not captured in our analysis.

5 CONCLUSION

The review of data mining scores and searches of the AERS database for Premarin Vaginal Cream did not identify any unlabeled adverse event terms for consideration as additions to the proposed labeling.

6 RECOMMENDATIONS

DDRE has no labeling recommendations based on this post-marketing safety review.

CONCURRENCE

Laura Governale, Pharm D., MBA
Drug Use Analysis Team Leader
Division of Epidemiology

7 REFERENCES

1. DuMouchel W, Pregibon D. Empirical bayes screening for multi-item associations. Proceedings of the conference on knowledge discovery and data; 2001 Aug 26-29; San Diego (CA): ACM Press: 67-76.

2. Szarfman A, Machado SG, O'Neill RT. Use of Screening Algorithms and Computer Systems to Efficiently Signal Higher-Than-Expected Combinations of Drugs and Events in the US FDA's Spontaneous Reports Database. Drug Safety 2002; 25:381-392.

APPENDICES

Appendix 1 – Proposed Product Labeling

The proposed product labeling for Premarin Vaginal Cream is available at the following location:

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Appendix 2 – Drug Utilization Data Tables

Table 1. Projected Number of Conjugated Estrogens Vaginal Cream Prescriptions Dispensed by U.S. Retail Pharmacies, 2002 - 2007, Stratified by Gender and Age

	2003	2004	2005	2006	2007
					(b) (4)

Table 2. Projected Number of Patients Receiving Conjugated Estrogens Vaginal Cream through U.S. Retail Pharmacies for the Years 2003-2007, Stratified by Gender

	2003	2004	2005	2006	2007
					(b) (4)

Appendix 3 – Drug Utilization Database Descriptions

IMS Health, IMS National Sales Perspectives™, Retail and Non-Retail

The IMS Health, IMS National Sales Perspective™ measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass Merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products moving from manufacturer into retail and non-retail settings in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections.

Verispan, LLC: Vector One®: National (VONA)

Verispan's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One receives over 2 billion prescription claims, representing over 160 million unique patients.

Prescriptions are captured from a sample of approximately 54,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent approximately 50% of retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

Verispan, LLC: Vector One®: Total Patient Tracker (TPT)

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies*, mass merchandisers, pharmacy benefits managers and their data systems. Vector one receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

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/s/

Adrienne Rothstein
3/12/2008 11:09:30 AM
CSO

Melissa Truffa
3/12/2008 12:33:21 PM
DRUG SAFETY OFFICE REVIEWER

Ann W McMahon
3/12/2008 01:40:49 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 18, 2008

TO: Wyeth Pharmaceuticals Inc.
Attention: Donald Lewis, Manager
Global Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19102-8299

FROM: George Lyght, R.Ph.
Sr. Regulatory Health Project Manager
Division of Reproductive & Urologic Products (DRUP) HFD-580

SUBJECT: **Memo to File**
NDA 20-216/S-060- Premarin (conjugated estrogens) Vaginal Cream – Information request by e-mail.

The Division requested the following information from Wyeth:

1. Clarification of the treatment group for subject (b) (6)
2. Copy of surgical report for subject (b) (6)
3. Copy of pathology report for subject (b) (6)

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/s/

George Lyght
7/23/2008 05:16:51 PM
CSO

George Lyght
7/23/2008 05:17:20 PM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 27, 2008

TO: Wyeth Pharmaceuticals Inc.
Attention: Donald Lewis, Manager
Global Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19102-8299

FROM: George Lyght, R.Ph.
Sr. Regulatory Health Project Manager
Division of Reproductive & Urologic Products (DRUP) HFD-580

SUBJECT: **Memo to File**
NDA 20-216/S-060- Premarin (conjugated estrogens) Vaginal Cream – Information request from Wyeth by e-mail.

RE: Modification of 4-month safety update For PVC NDA 20,216/060

Using the last information sent to us, we will modify Table 8-1 in the 4-Month Safety Update to indicate that 110 PVC 21/7 subjects (not 109) discontinued the open-label phase, and that the loss to follow-up numbers in the open-label phase, across the 4 treatment groups, are 19, 9, 13, and 9, respectively.

Confirm that this modification is correct.
We are requesting two points of data clarification. 1. In the 4-Month Safety Update, Table 8-1 shows that 13 subjects discontinued due to an adverse event during the double-blind phase and that 13 subjects discontinued due to an adverse event in the open-label phase. However Table 10-4 in the 4-Month Safety update shows that 15 subjects reported adverse event as reason for discontinuation in the double-blind phase and 13 subjects reported adverse event as reason for discontinuation during the open label phase. There are 26 narratives in the submission confirming discontinuations. We believe that Subject (b) (6) appears in the listing under both the double-blind and open-label phase. Do clarify. 2. Clarify the 11 subjects who appear in the follow-up study phase in Table 10-4. They appear to consist of subject who discontinued in either the double-blind or open-label phases of treatment.

Another request for information. Provide a copy of the report of the pelvic scan performed for Subject (b) (6) on 30Nov05 . The narrative on this subject does not indicate the findings. Provide a copy of the "consultation with a hematologist" or any other healthcare provider.

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/s/

George Lyght
7/23/2008 05:14:32 PM
CSO

George Lyght
7/23/2008 05:15:01 PM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 21, 2008

TO: Wyeth Pharmaceuticals Inc.
Attention: Donald Lewis, Manager
Global Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19102-8299

FROM: George Lyght, R.Ph.
Sr. Regulatory Health Project Manager
Division of Reproductive & Urologic Products (DRUP) HFD-580

SUBJECT: **Memo to File**
NDA 20-216/S-060- Premarin (conjugated estrogens) Vaginal Cream – Information request from Wyeth by e-mail.

RE: Population tables

Two additional tables using the same population you have identified in the data submitted for most bothersome symptom as meeting the 3 specified inclusion criteria, namely n=93 for PVC 21/7, n=51 for Placebo 21/7, n=98 for PVC 2x/wk, and N=48 for Placebo. 2x/wk. One table should show the mean change in superficial and parabasal cells with p-value for both. The second table should show the mean change in vaginal pH.

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

/s/

George Lyght
7/23/2008 05:02:38 PM
CSO

George Lyght
7/23/2008 05:05:01 PM
CSO

Filing Memorandum Addendum
Division of Reproductive and Urologic Products

Supplement NDA 20-216/SE2-060

Trade Name:	**Premarin ® Vaginal Cream (0.625 mg/g Premarin ® Vaginal Cream)**
Generic Name:	**Conjugated estrogens, USP**
Applicant:	**Wyeth Pharmaceuticals Inc. P.O. Box 8299 Philadelphia, PA 19101-8299**
Classification:	**3S**
Submission date:	**September 25, 2007**
Indication:	**"Treatment of vulvar vaginal atrophy (VVA), dyspareunia associated with VVA or kraurosis vulvae."**
Study Protocol:	**Phase 3b Protocol 0713S5-413-NA, "Efficacy and Safety of 2 Low-Dose Regimens of Conjugated Estrogen Cream Administered Vaginally in Postmenopausal Women With Atrophic Vaginitis"**
Dosage Form:	**Vaginal cream**
Dosage Strengths:	**0.3 mg (0.5 gram of 0.625 mg/gram vaginal cream)**
Dosing Regimens:	**1) 0.3 mg (0.5 gram) Premarin® Vaginal Cream daily for 21 days, then 7 days off (PVC 21/7) 2) 0.3 mg (0.5 gram) Premarin® Vaginal Cream twice weekly (Monday and Thursday) (PVC 2x/wk)**
Related Submission:	**IND 72,606**
Filing Meeting:	**November 6, 2007**
74-Day Letter:	**December 8, 2007**
Labeling:	**April 25, 2008**
Clinical Review Date:	**May 16, 2008**
User Fee Goal Date:	**July 25, 2008**
Medical Reviewer:	**Theresa H. van der Vlugt, MD, M.P.H.**

Background:

On November 6, 2007, Wyeth Pharmaceuticals Inc. was requested to provide the following information (or indicated where such information can be located in the eCTD submission) to assist in determining the need for a Division of Scientific Investigation (DSI) audit:

- Number of subjects randomized per center.
- Number of subjects treated per center.
- Number of subjects discontinued per center.
- Number of protocol violations per center.

- Number of major protocol violations per center.

Wyeth Pharmaceutical Inc. responded on November 21, 2007. Thirty-three (33) U.S. sites participated in the primary Phase 3 clinical trial; 213 subjects (49.4%, 213 of 431 subjects) were randomized at 27 U.S. sites (6 of the 33 sites did not randomize any subjects). Sixteen (16) Canadian sites participated in the primary Phase 3 clinical trial; 218 subjects (50.6%, 218 of 431 subjects) were randomized at 15 Canadian sites (1 site did not randomize any subjects).

At the 27 active U.S. sites, the number of subjects per site ranged from 1 to 20. At the 15 active Canadian sites, the number of subjects per site ranged from 3 to 36. A total of 5 subjects were not treated at U.S. sites (2.3%, 5 of 213 randomized subjects). A total of 3 subjects were not treated at Canadian sites (1.4%, 3 of 218 randomized subjects).

Per the submission, a total of 29 subjects discontinued during the double-blind phase of Study 0713S5-413-NA (6.8%, 29 of 423 treated subjects). The most common reasons for discontinuation were adverse events (13 subjects, 3.1%) and subject request (12 subjects, 2.8%). Serious adverse events in the active treatment groups included 1 case of acute and chronic cholecystitis (PVC 2x/wk), 1 case of carcinoma of the kidney (PVC 2x.wk), and 1 case of intracranial aneurysm (placebo 2x/wk).

As of the snapshot date of April 11, 2007 (which includes both the 12-week double-blind phase and a portion of the open-label phase of Study 0713S5-413-NA), a total of 79 treated subjects (18.7%, 79 of 423 treated subjects) discontinued Study 0713S5-413-NA. Forty-eight (48) subjects discontinued at U.S. sites (23.1%, 48 of 208 treated subjects). The number of treated subjects discontinuing per U.S. sites ranged from 1 to 6 (6 of 18 treated subjects [33.3%] discontinued at Site # 015 [Dr. William Koltun, Medical Center for Clinical Research, San Diego, CA]). Five (5) subjects discontinued (33.3%, 5 of 15 treated subjects) from U.S. Site # 017 (Dr. Barry Lubin, Hampton Rhodes Center for Clinical Research, Inc., Norfolk, VA). Thirty-one (31) subjects discontinued at Canadian sites (14.4%, 31 of 215 treated subjects). The number of subjects discontinuing per Canadian site ranged from 1 to 7 (7 of 36 treated subjects [19.4%] discontinued at Site # 037 [Dr. Celine Bouchard, Centre Medical Berger, Quebec, Canada]).

Per the submission, a total of 33 subjects had protocol violations or deviations during the 12-week double-blind phase of Study 0713S5-413-NA (7.6%, 33 of 431 randomized subjects). The most common reason for a protocol violation or deviation was over or under compliance with study medication administration (2.5%, 11 of 431 randomized subjects.

As of the snapshot date of April 11, 2007, a total of 36 protocol violations or deviations were reported (8.3%, 36 of 431 randomized subjects). The number of protocol violations or deviations across all U.S. sites ranged from 1 to 4 (4 of 19 randomized subjects [21.0%] at U.S. Site # 015 [Dr. William Koltun, Medical Center for Clinical Research, San Diego, CA], 3 of 8 randomized subjects (37.5%) at U.S. Site # 011 (Dr. Janet Gersten, New Age Medical Research Corporation, Miami, Fl), and 2 of 15 randomized

subjects (13.3%) at U.S. Site # 017 (Dr. Barry Lubin, Hampton Rhodes Center for Clinical Research, Inc., Norfolk, VA). The number of protocol violations or deviations across all Canadian sites ranged from 1 to 4 (4 of 36 randomized subjects [11.1%] at Canadian Site # 037).

Medical Officer's Comments:

Overall, the 15 active Canadian sites and the 27 active U.S. sites randomized approximately the same number of subjects for Study 0713S5-413-NA (213 versus 218, respectively). However, the Canadian sites had an overall larger concentration of patients per site (range of 3 to 36 versus a range of 1 to 20 for the U.S. sites).

The number of discontinuation per U.S. sites ranged from 1 to 6 versus 1 to 7 per Canadian sites. Protocol violations or deviations ranged from 1 to 4 per U.S. sites and 1 to 4 per Canadian sites. The reported numbers of protocol violations or deviations do not appear to be excessive.

One U.S. site (Site # 15 in San Diego, CA) reported 6 discontinuations in 18 treated subjects (33.3%) and 4 protocol violations (21.0%, 4 in 19 randomized subjects). Dr. William Koltun was the Principle Investigator at this site. Dr. Koltun is well known by this Division having participated in 120 INDs in the Agency's database and inspected in connection with NDAs reviewed in years 2000, 2004, and 2006. Per the Good Clinical Practice Branch of DSI, the three mentioned inspections were classified as VAI. One other U.S. site, Site # 017, reported 33.3% discontinuations and 13.3% protocol violations. Dr. Barry Lubin was the Principle Investigator at this site. While Dr. Lubin has participated in 134 INDs he has not been previously inspected by DSI.

In addition, 1 Canadian site, Site # 037 (Dr. Celine Bouchard, Centre Medical Berger, Quebec, Canada) reported 7 discontinuations (19.4%, 7 of 36 treated subjects) and 4 protocol violations (11.1%, 4 of 36 randomized subjects). Dr. Bouchard has participated in 12 INDs but has not been previously inspected by DSI.

While no immediate concerns regarding data integrity are evident in the information provided in the submission, or in the requested information provided by Wyeth on November 21, 200, the clinical data presented in this submission represents the first clinical information available for Premarin® Vaginal Cream since its initial development and labeling in 1949 for "the treatment of atrophic vaginitis and kraurosis vulvae.".

This reviewer recommends that U.S. Site # 017 in Norfolk, VA and Canadian Site # 037 in Quebec, Canada be inspected by DSI.

Recommendations for a Division of Scientific Investigations (DSI) Audit:

Two sites participating in Study 0713S5-413-NA are recommended for a DSI inspection:

1. Dr. Barry Lubin
   Hampton Rhodes Center for Clinical Research, Inc.
   885 Kempsville Road
   Suite 221
   Norfolk, VA 23502

2. Dr. Celine Bouchard
   Clinique RSF Inc.
   Center Medical Berger
   1000, chemin Sainte-Foy
   Bureau 102
   Quebec
   Canada
   G1S 2L6

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

/s/

Theresa Van Der Vlugt
12/5/2007 11:57:09 AM
MEDICAL OFFICER

Shelley Slaughter
12/5/2007 02:36:07 PM
MEDICAL OFFICER
I concur.

Filing Memorandum
Division of Reproductive and Urologic Products

Supplement NDA 20-216/SE2-060

Trade Name:	**Premarin ® Vaginal Cream (0.625 mg/g Premarin ® Vaginal Cream)**
Generic Name:	**Conjugated estrogens, USP**
Applicant:	**Wyeth Pharmaceuticals Inc. P.O. Box 8299 Philadelphia, PA 19101-8299**
Classification:	**3S**
Submission date:	**September 25, 2007**
Indication:	**"Treatment of vulvar vaginal atrophy (VVA), dyspareunia associated with VVA or kraurosis vulvae."**
Study Protocol:	**Phase 3b Protocol 0713S5-413-NA, "Efficacy and Safety of 2 Low-Dose Regimens of Conjugated Estrogen Cream Administered Vaginally in Postmenopausal Women With Atrophic Vaginitis"**
Dosage Form:	**Vaginal cream**
Dosage Strengths:	**0.3 mg (0.5 gram of 0.625 mg/gram vaginal cream)**
Dosing Regimens:	**1) 0.3 mg (0.5 gram) Premarin® Vaginal Cream daily for 21 days, then 7 days off 2) 0.3 mg (0.5 gram) Premarin® Vaginal Cream twice weekly (Monday and Thursday)**
Related Submission:	**IND 72,606**
Filing Meeting:	**November 6, 2007**
74-Day Letter:	**December 8, 2007**
Clinical Review Date:	**May 16, 2008**
Labeling:	**June 13, 2008**
User Fee Goal Date:	**July 25, 2008**
Medical Reviewer:	**Theresa H. van der Vlugt, MD, M.P.H.**

Submission Background:

Premarin® (Conjugated estrogens, USP) Cream was initially marketed in 1946 under NDA 05-900 for vaginal use for atrophic vaginitis and for topical use for acne vulgaris. In 1949, Premarin® Vaginal Cream was developed and labeled in "the treatment of atrophic vaginitis and kraurosis vulvae[1]". Premarin® Cream was relabeled for the acne

[1] Dorland's Illustrated Medical Dictionary, twenty-sixth edition, 1981: Kraurosis = a dry, shriveled condition of a part, especially of the vulva; Vulvae = an atrophic disease affecting the female external

vulgaris indication only, but was withdrawn from the market in 1976 when "found to be less than effective for acne vulgaris".

In a *Federal Register* notice (DESI 2238; Docket No. FDC-D-500 [now Docket No. 76N-0261]) published in July 27, 1972 (37 FR 15028), the FDA announced its conclusion that various drug products, including Premarin® Vaginal Cream was effective in the treatment of atrophic vaginitis and kraurosis vulvae. Ayerst Laboratories, a Division of the American Home Products Corp., now Wyeth Pharmaceutical Inc., filed ANDA 83-273 for Premarin® Vaginal Cream on October 3, 1972. ANDA 83-273 was subsequently approved on October 16, 1978 (0.625 mg of conjugated estrogens, USP per gram of cream). Approved dosages ranged from 0.5 grams (approximately 0.3 mg of conjugated estrogens) to 2 grams (1.25 mg of conjugated estrogens) applied cyclically, daily for three weeks, then one week off. In 1991, ANDA 83-273 was renumbered to NDA 20-216 when the Division of Metabolic and Endocrine Products (DMEP) assumed responsibility for Premarin® Vaginal Cream.

Premarin® Vaginal Cream (PVC) contains a mixture of conjugated estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, as sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin.

Phase 3b Protocol 0713S5-413-NA entitled, "Efficacy and Safety of 2 Low-Dose Regimens of Conjugated Estrogen Cream Administered Vaginally in Postmenopausal Women With Atrophic Vaginitis" was a prospective study conducted at 49 sites in Canada (17 sites) and the U.S. (32 sites) whereby each subject was treated for 12 weeks with either PVC or matching placebo (double-blind treatment period). An additional 40 weeks of treatment (open-label treatment period; all subjects received PVC) followed the initial 12 weeks of double-blind treatment. The data submitted in Supplement-060 is an interim report that describes the efficacy and safety after the first 12 weeks of treatment.

The primary objective of Study 0713S5-413-NA, originally submitted on June 16, 2005 under IND 72,606, was to evaluate the efficacy of two 0.3 mg (0.5 grams) dosing regimens of Premarin® Vaginal Cream (0.625 mg of conjugated estrogens per gram of vaginal cream) in the treatment of atrophic vaginitis as the change from baseline in the percent of superficial cells on a vaginal maturation index (VMI) at 12 weeks of treatment. The proposed active and placebo dosing regimens were:

A1 = 0.3 mg Premarin® Vaginal Cream (0.5 grams containing 0.625 mg of conjugated estrogens per gram) inserted vaginally daily for 21 days, then off for 7 days (28 day cycle), repeated for two additional 28 day cycles (total of 84 days).

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genitalia, resulting in drying and shriveling of the parts, and marked by leukoplakic patches on the mucosa, itching, dyspareunia, dysuria, and soreness.

A2 = 0.5 grams of placebo vaginal cream inserted vaginally daily for 21 days, then off for 7 days (28 day cycle), repeated for two additional 28 day cycles (total of 84 days).
B1 = 0.3 mg Premarin® Vaginal Cream (0.5 grams containing 0.625 mg of conjugated estrogens per gram) inserted vaginally on Monday and Thursday of each week for 12 weeks (total of 84 days).
B2 = 0.5 grams of placebo vaginal cream inserted vaginally on Monday and Thursday of each week for 12 weeks (total of 84 days).

The secondary objectives of Study 0713S5-413-NA were to:

- evaluate change from baseline in the percent of superficial cells on a vaginal maturation index at 4, 6, and 52 weeks;
- evaluate the effects of both Premarin® Vaginal Cream dosing regimens on symptom relief, as assessed by weekly symptom composite score through 12 weeks;
- evaluate the effects of both Premarin® Vaginal Cream regimens on endometrial stimulation at 52 weeks; and to
- evaluate the effects of both Premarin® Vaginal Cream regimens on Genital Health Clinical Evaluation (GHCE) at 4, 6, 12, and 52 weeks.

In a letter dated September 1, 2005, the Division provided Wyeth Pharmaceuticals Inc. with numerous comments and recommendations regarding Study 0713S5-413-NA. In particular, Wyeth Pharmaceuticals Inc. was advised that "For the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associate with the menopause, the Agency recommends three co-primary endpoints:

- Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome to her. For study inclusion, study participants would have self-identified at least one moderate to severe vulvar and vaginal atrophy symptom. The primary efficacy analysis should show statistically significant improvement in the moderate to severe symptom identified by the subject as most bothersome.
- Mean change from baseline to week 12 in vaginal pH. For study inclusion, study participants would have a vaginal pH > 5.0. The primary efficacy analysis should show a statistically significant lowering of vaginal pH.
- Mean change from baseline to week 12 in vaginal maturation index (proportions of superficial and parabasal cells). For study inclusion, study participants would have no greater than 5 percent superficial cells on a vaginal smear. The primary efficacy analysis should show a statistically significant increase in superficial cells and a statistically significant decrease in parabasal cells."

Wyeth Pharmaceuticals Inc. responded on October 14, 2005 (S-002) with the following proposed changes to Study 0713S5-413-NA:

<u>Clinical:</u>

1. "Change the primary endpoint for VMI to demonstrate a statistically significant increase in superficial cells and a statistically significant decrease in parabasal cells.
2. Include 2 additional co-primary endpoints, change in baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome to her and change in baseline to week 12 in vaginal pH.
3. Change the inclusion criterion to a reading of vaginal pH $\geq$ 5.
4. Require an endometrial biopsy for all subjects at week 52; a biopsy at early termination for any patient who terminates after week 12; or who experiences abnormal vaginal bleeding at anytime during the study."

Statistical:

1. "Revise the statistical methods section so that each treatment group will be compared to the matching placebo group."
2. "Reviewed the proposed sample size for Study 0713S5-413-NA." Available data on the effects of PVC on dyspareunia (submitted to IND 21,696), suggested mean differences from placebo of approximately 8% in superficial cells, 0.5 pH units, and 0.45 units on a symptom scale of 0 to 3. From this data, Wyeth Pharmaceuticals Inc. concluded that the proposed sample size for Study 0713S5-413-NA had approximately 99%, 86% and 84% power, respectively, to detect these differences. Thus, the proposed sample size was not changed.

Chemistry:

1. "A certificate of Analysis for the placebo was provided.
2. There is no API added in any amount in the placebo cream.
3. Provided side by side comparison of the quantitative formulation for the placebo and active drug product."

On February 23, 2006, Study 0713S5-413-NA was amended (Amendment 1, S-009) to include the following:

Primary endpoints:

1. "Change from baseline in VMI (% superficial and parabasal cells) at week 12.
2. Change from baseline in the vaginal pH at week 12.
3. Change from baseline in the severity of most bothersome symptom at week 12."

Secondary endpoints:

1. Change from baseline in superficial and parabasal, vaginal pH at weeks 4, 6 and 52 and the most bothersome symptom from week 1 through week 12.
2. Change from baseline DHCE (General Health Clinical Evaluation) score where score is the sum of: vaginal pH, fluid secretion, epithelial mucosa, moisture,

vaginal rugosity, and mucosa color. Total score defined as the sum of six parameters. Change from baseline in total score will be derived at weeks 4, 6, 12 and 52.

3. Change from baseline weekly composite symptom score where a weekly composite score will be estimated as the average of the daily composite scores over each 7 day period.

Study 0713S5-413-NA was again amended on February 8, 2007 (Amendment 2, S-023) to include the following:

1. "Additional blood samples to be collected at visits 6 or 7 (weeks 26 and 52) at selected sites to measure serum estrone and estradiol levels."

The statistical analysis plan (SAP) for Study 0713S5-413-NA was submitted on March 19, 2007. An amendment to the SAP was submitted on April 24, 2007 (S-028). Per this submission, the SAP was amended on April 4, 2007 and Study 0713S5-413-NA was unblinded on April 9, 2007. The revision for change from baseline of the most bothersome symptom included the addition of the following paragraph:

"To assess the sensitivity of this endpoint, an alternate definition of the baseline score will be defined. This alternate definition will be the severity score recorded for the most bothersome symptom at the screening visit. The change from baseline will be calculated using this baseline value and analyzed similarly to the primary definition."

Clinical Safety and Effectiveness:

Study 0713S5-413-NA was a prospective, randomized, placebo-controlled, double-blind study. A total of 431 subjects met the inclusion and exclusion criteria at screening. Of these 431 screened subjects, 423 subjects were randomly assigned (using a Clinical Randomization/Enrollment System [CORE]) to one of the four treatment groups as shown below. Three hundred ninety-four (394) subjects completed the 12-week double-blind treatment period.

Treatment Group (number of subjects treated/completed	**Regimen**
A1(143/129)	0.3 mg (0.5 gram) PVC daily for 21 days, then 7 days off (PVC-21/7)
A2 (72/69)	0.5 gram placebo cream daily for 21 days, then 7 days off (Placebo-21/7)
B1 (140/132)	0.3 mg (0.5 gram) PVC twice weekly on Monday and Thursday (PVC-2x/wk)
B2 (68/64)	0.5 gram placebo cream twice weekly on Monday and Thursday (Placebo-2x/wk)

Effectiveness analyses:

The primary analysis was based on the last-observation-carried-forward (LOCF) data from the MITT population at week 12. The MITT population was defined as all randomly assigned subjects who recorded at least 1 application of test article and had a baseline value and at least 1 follow-up value for the three primary efficacy variables (changes in VMI [percentages of superficial and parabasal cells on a vaginal cytology smear], vaginal pH, and most bothersome vaginal symptom). For most bothersome symptom, each subject identified 1 of 4 symptoms (vaginal dryness, itching, burning, and dyspareunia) at screening as most bothersome to her. Each subject recorded the severity of each of the 4 symptoms daily on a diary card using the following scores: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 5 = not applicable and 9 = not done. Weekly symptom scores were derived from the average of all daily scores recorded during a 7-day period (excluding scores of 5, not applicable, and 9, not done). At screening the subjects identified which of the 4 symptoms was the most bothersome.

Per the submission, treatment with PVC-21/7 or PVC-2x/wk significantly increased the mean percentage of superficial cells from baseline to week12 and significantly decreased the mean percentage of parabasal cells ($p < 0.001$ for both cell types), treatment with PVC-21/7 or PVC-2x/wk significantly decreased vaginal pH from baseline to week 12 ($p < 0.001$), and treatment with PVC-21/7 or PVC-2x/wk significantly reduced the score (composite score) for the most bothersome symptom from baseline to week 12 ($p \leq 0.001$).

The mean change in individual vulvar and vaginal atrophy symptoms (dryness, itching, burning, and dyspareunia) are reported as secondary endpoints in the submission. Per the submission, a statistically significant difference (PVC-21/7 versus placebo) between baseline and week 12 was reported for vaginal dryness and dyspareunia for the PVC-21/7 dosing regimen ($p < 0.030$). A statistically significant difference (PVC-2x/wk versus placebo) between baseline and week 12 was reported for painful intercourse for the PVC-2x/wk dosing regimen ($p < 0.010$).

Clinical safety:

All subjects, including those randomized to placebo, continued in an open-label extension for safety for 40 additional weeks after completing the 12-week double-blind treatment period of Protocol 0713S5-413-NA,. In the 40-week open-label extension, all subjects received PVC at the same dosing regimen which they were randomly assigned in the double-blind portion of the study as shown below.

Double-Blind Treatment Group	**Open-Label Treatment Group**	**Open-Label Regimens**
A1[1] or A2[2]	A1[1]	0.3 mg (0.5 grams) PVC for 21 days, 7 days off
B1[3] or B2[4]	B1[3]	0.3 mg (0.5 grams) PVC twice weekly on Monday and Thursday

[1] A1 = 0.5 grams of PVC (0.3 mg) inserted vaginally daily for 21 days, then off for 7 days.

[2] A2 = 0.5 grams of placebo vaginal cream inserted vaginally daily for 21 days, then off for 7 days.

[3] B1 = 0.5 grams of PVC (0.3 mg) inserted vaginally on Monday and Thursday of each week for 12 weeks.
[4] B2 = 0.5 grams of placebo vaginal cream inserted vaginally on Monday and Thursday of each week for 12 weeks.

Per the submission, safety information in this supplement includes data from the 12-week double-blind treatment period of the study as well as preliminary safety information from the ongoing 40-week open-label treatment period through April 11, 2007 (safety snapshot date). Safety information, including endometrial safety data, at 52 weeks will be submitted with the 4-month safety update.

Twenty-nine (29 [6.9%]) subjects (out of a total of 423 randomized subject) discontinued from Study 0713S5-413-NA during the 12-week double-blind treatment period. Overall, the most common reasons for discontinuation during the 12-week double-blind treatment period were adverse events (3.1%, 13 of 423 subjects) and subject request (2.8%, 12 of 423 subjects). The most common treatment-emergent adverse events were headache (14.7%, 62 of 423 subjects), infection (7.8%, 33 of 423 subjects), abdominal pain and back pain (6.6% each; 28 and 28 of 423 subjects, respectively), and accidental injury, pain and vaginitis (5% each; 21 of 423 subjects, respectively). No subjects have died as of the snapshot date (April 11, 2007).

This submission is provided entirely in the eCTD format.

The request for a pediatric waiver is included in the submission. A pediatric waiver should be granted.

Per the submission, periodic monitoring of each clinical study contained in the submission was performed in accordance with the Wyeth Research Standard Operating Procedures (SOPs) in effect during the time the studies were active. The purpose of this review was to verify the accuracy of the case report forms submitted to Wyeth research. No further information regarding disclosure of study audits is provided.

Fileability of sNDA 20-216/SE2-060:

sNDA 20-216/SE2-060 is fileable.

Effectiveness Review Issues:

1. Wyeth Pharmaceuticals Inc. calculated the mean change from baseline to week 12 (or last visit) in subject's most bothersome moderate to severe vulvar and vaginal atrophy symptom score (composite score) as one of the co-primary efficacy variables. However, the mean change from baseline in subject's self-assessment of each individual vaginal symptom is presented as secondary efficacy variables.

2. Data submitted in primary Phase 3b Study 0713S5-413-NA reports a mean raw score at baseline of less than 2.0 for vaginal dryness (mixed model analysis) as shown below:

   PVC 21/7 (n = 120) mean raw score = 1.69
   Placebo 21/7 (n = 61) mean raw score = 1.92
   PVC 2x/wk (n = 116) mean raw score = 1.87
   Placebo 2x/wk (n = 62) mean raw score = 1.79

Safety Review Issues:

No safety review issues have been identified at this time.

Labeling Review Issues:

1. Wyeth Pharmaceuticals Inc. is requesting the approval of both dosage regimens, 0.3 mg PVC-21/7 and 0.3 mg PVC 2x/wk, for the "treatment of dyspareunia associated with VVA" while retaining the currently approved indications "treatment of atrophic vaginitis and kraurosis vulvae" for the following dosage range: 0.5 gram (0.3 mg) to 2.0 gram (1.25 mg) daily, three weeks on and 1 week off.

Request for Data:

1. Wyeth Pharmaceuticals Inc. was requested to submit, in tabular format, the following information for Study 0713S5-413-NA for the MITT population using LOCF:

   1. The number of subjects in each treatment group who, at baseline, met the following three co-primary endpoints:

      - Self-identified at least one moderate to severe vulvar and vaginal atrophy symptom (severity score of 2.0 or greater for vaginal dryness, vaginal itching, vaginal burning, or dyspareunia) that was also self-identified as most bothersome;
      - Had a baseline vaginal pH of 5 or greater; and
      - Had no more than 5 percent superficial cells on a vaginal smear.

   2. The mean change (SD) between baseline and week 12 for each individual moderate to severe symptom identified as most bothersome for each treatment group for subjects who at baseline met the criteria as specified in number 1 above for most bothersome symptom, vaginal pH, and superficial cells.

   3. The p-value (active treatment versus placebo) at week 12 for each individual symptom as delineated in number 2 above.

2. Wyeth Pharmaceuticals Inc. was requested to provide the following information (or indicated where such information can be located in the eCTD submission) to assist in determining the need for a DSI audit:

   - Number of subjects randomized per center.
   - Number of subjects treated per center.
   - Number of subjects discontinued per center.
   - Number of protocol violations per center.
   - Number of major protocol violations per center.

Recommendations for a Division of Scientific Investigations (DSI) Audit:

This will be provided upon receipt of the requested information.

Review of Financial Disclosure Documents:

Form FDA 3454 (4/06), dated September 13. 2007, and signed by Gary L. Stiles, MD, Executive Vice President and Chief Medical Officer and Gary Gallagher, Vice President – R & D Finance, Wyeth Pharmaceuticals Inc. was included in the submission. Nine of the of the 49 listed principal investigators for Study 0713A5-413-NA was the recipient of significant payment of other sorts as defined in 21 CFR 54.2(f) – "any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;"

U.S. Investigator:

Canadian Investigator:

Comments for the Applicant:

From the data submitted in primary Phase 3b Study 0713S5-413-NA, we are concerned that the efficacy mixed model analysis reports a mean raw score at baseline of less than 2.0 for vaginal dryness:

PVC 21/7 (n = 120) mean raw score = 1.69
Placebo 21/7 (n = 61) mean raw score = 1.92
PVC 2x/wk (n = 116) mean raw score = 1.87
Placebo 2x/wk (n = 62) mean raw score = 1.79

Per the Agency's 2003 draft Guidance for Industry, for study inclusion, study participants would have self-identified at least one moderate (score of 2) to severe (score of 3) vulvar and vaginal atrophy symptom.

NDA: 21-813

45 Day Filing Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?	X		
2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
3) On its face, is the clinical section of the NDA legible so that substantive review can begin?	X		
4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	X		
5) On its face, do there appear to be the requisite number of adequate and well controlled studies in the application?	X		
6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	X		
7) Are all data sets for pivotal efficacy studies complete for all indications (infections) requested?	X		
8) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X		.

ITEM	YES	NO	COMMENT
9) Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?	X		
10) Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X		
11) Has the applicant submitted all additional required case record forms (beyond deaths and drop-puts) previously requested by the Division	X		
12) Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?	X		
13) Has the applicant presented safety assessment based on all current world-wide knowledge regarding this product?	X		
14) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?	X		
15) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	X		
16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	X		
17) Reasons for refusal to file:			

Theresa H. van der Vlugt, MD, M.P.H.
Medical Officer
Division of Reproductive and Urologic Products

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

/s/

Theresa Van Der Vlugt
11/21/2007 01:04:28 PM
MEDICAL OFFICER

Shelley Slaughter
11/21/2007 03:41:44 PM
MEDICAL OFFICER
I concur.