Ovarian Ca Screen Could Detect Early Disease

BY DOUG BRUNK

FROM AN AMERICAN SOCIETY OF CLINICAL ONCOLOGY PRESSCAST

A staged algorithm that incorporates the CA-125 assay to screen postmenopausal women for ovarian cancer has a near-perfect specificity of 99.9%, according to a single arm, multicenter study that enrolled more than 3,200 women at average risk of the disease.

If confirmed in larger studies, this approach could be used to detect ovarian cancer in its early, more curable stages, lead author Dr. Karen Lu said.

"Ovarian cancer is the most lethal gynecologic cancer," said Dr. Lu, professor of gynecologic oncology at the University of Texas M.D. Anderson Cancer Center, Houston. "Greater than 75% of cases present with advanced stage disease, when cure rates are less than 30%. If caught at an early stage, cure rates are 60%-90%, but at the current time there are no effective screening methods."

For the 9-year study, scheduled to be presented during ASCO's annual meeting in Chicago, Dr. Lu and her associates enrolled 3,252 women aged 50-74 years with no significant family history of breast or ovarian cancer to be screened with the Risk of Ovarian Cancer Algorithm (ROCA). She described ROCA as a mathematical model that takes into account a woman's age as well as changes in the values of her CA-125 assay over time.

"From here there are three possibilities," she explained. "Those individuals who have a low ROCA score are told to come back at 1 year for a repeat CA-125. Those who have an intermediate ROCA score are told to come back at 3 months for another CA-125, and those who have a high ROCA score are triaged to a trans-

PREMARIN® (CONJUGATED ESTROGENS) VAGINAL CREAM

BRIEF SUMMARY: See Package Insert for Full Prescribing Information. For further product information and current package insert, please visit www.premarinvaginalcreamhcp.com or call our medical communications department toll-free at 1-800-934-5556.

WARNING: CARDIOVASCULAR DISORDERS, ENDOMETRIAL CANCER, BREAST CANCER and PROBABLE DEMENTIA

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) in full Prescribing Information]*.

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) in full Prescribing Information]*.

The WHI 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 full Prescribing Information]*.

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.

ESTROGEN PLUS PROGESTIN THERAPY

CARDIOVASCULAR DISORDERS AND PROBABLE DEMENTIA

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) in full Prescribing Information]*.

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) in full Prescribing Information]*.

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 full Prescribing Information]*.

BREAST CANCER

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) in full Prescribing Information]*.

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.

INDICATIONS AND USAGE

Treatment of Atrophic Vaginitis and Kraurosis Vulvae

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

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

WARNINGS AND PRECAUTIONS

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.

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) in full Prescribing Information]*. 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).

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) in full Prescribing Information]*. The increase in risk was demonstrated after the first year and persisted.

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 *[see Clinical Studies (14.2) in full Prescribing Information]*.

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).

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). 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 full Prescribing Information]*.

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 *[see Clinical Studies (14.2) in full Prescribing Information]*. 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 *[see Clinical Studies (14.2) in full Prescribing Information]*. 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.

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] [see Clinical Studies (14.2) in full Prescribing Information]*.

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. 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) in full Prescribing Information]*.

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. 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.

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-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 *[see Use in Specific Populations (8.3), and Clinical Studies (14.3) in full Prescribing Information]*.

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.

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 *[see Use in Specific Populations (8.3), and Clinical Studies (14.3) in full Prescribing Information]*.

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 *[see Use in Specific Populations (8.5), and Clinical Studies (14.3) in full Prescribing Information]*.

Gallbladder Disease

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

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.

(continued on next page)

VITALS

Major Finding: The specificity of a new screening approach developed for postmenopausal women at average risk for ovarian cancer was 99.9%.

Data Source: A single arm, prospective, multi-center study of 3,252 women aged 50-74.

Disclosures: One of the study authors, Dr. Herbert A. Fritsche, disclosed that he received research funding from Roche Diagnostics. Another study author, Dr. Robert C. Bast, Jr., disclosed that he serves as a consultant and advisor to Fujiresio Diagnostics, Inc. He also receives other remuneration and royalties for helping to invent the CA-125 assay.

vaginal ultrasound and referral to a gynecologic oncologist."

After following the women for 9 years the researchers found that the average annual rate of referral for CA-125 assays every 3 months was 6.8% and that the average annual rate of transvaginal ultrasound and referral to a gynecologic oncologist was only 0.9%. "Each year the overwhelming majority of women were triaged to the low-risk category—an annual CA-125," Dr. Lu said.

Cumulatively, 85 women (2.6%) received transvaginal ultrasound and subsequent referral to a gynecologic oncologist. Of these, eight required surgery: three for invasive ovarian cancers (two stage 1C and one stage IIB), two for borderline ovarian tumors, and three for benign ovarian tumors. This translated into a positive predictive value of 37.5%. "This means that three operations would be necessary to detect one case of invasive ovarian cancer," she said.

The combined specificity of ROCA followed by transvaginal ultrasound was 99.9%, "which means that there were very few false positive."

Dr. Lu emphasized that while results of the ROCA screening strategy are encouraging, "they are not practice changing at this time. We need to await the results of a definitive ovarian cancer screening trial that uses mortality as an end point, and uses the same ROCA algorithm." That trial of more than 200,000 women is underway in the United Kingdom, she said. Results are expected in 2015.

ASCO President Dr. Douglas W. Blayney said that the ROCA algorithm "represents yet another example of personalized medicine. Here, we have a personalized screening strategy for a vicious type of cancer. This also represents a more refined application of known technology. The CA-125 is widely available, as is transvaginal ultrasound, which is intrusive and technologically somewhat difficult to interpret. Here, we have a staged application." ■

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.

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.

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.

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.

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.

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.

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.

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

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.

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.

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.

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.

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.

ADVERSE REACTIONS
The following serious adverse reactions are discussed elsewhere in the labeling:
- Cardiovascular Disorders *[see Boxed Warning, Warnings and Precautions (5.2)]*
- Endometrial Cancer *[see Boxed Warning, Warnings and Precautions (5.3)]*

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) in full Prescribing Information]*.

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.

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.

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

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.

USE IN SPECIFIC POPULATIONS

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.

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.

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

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 full Prescribing Information]*.

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

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 women receiving estrogen-alone or estrogen plus progestin when compared to placebo *[see Clinical Studies (14.3) in full Prescribing Information]*.

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

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

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

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

This brief summary is based on PREMARIN Vaginal Cream Prescribing Information W10413C018 ET01, Rev 11/09.

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Pfizer

FDA Warns on Fracture Risks With PPIs

The Food and Drug Administration issued a warning to physicians and consumers that proton pump inhibitors may increase the risk of hip, wrist, and spine fractures.

The agency said that it is changing the labeling for prescription and over-the-counter versions of proton pump inhibitors (PPIs) to reflect new safety information that is the result of a review of seven epidemiologic studies. Most of the observed risk was in people older than age 50 years and those who took high doses or used the drugs for more than a year. Prescription PPIs include esomeprazole (Nexium), dexlansoprazole (Dexilant), omeprazole (Prilosec, Zegerid), lansoprazole (Prevacid), pantoprazole (Protonix), and rabeprazole (Aciphex). There are OTC versions of Prilosec, Zegerid, and Prevacid.

"Because these products are used by a great number of people, it's important for the public to be aware of this possible increased risk and, when prescribing proton pump inhibitors, health care professionals should consider whether a lower dose or shorter duration of therapy would adequately treat the patient's condition," said Dr. Joyce Korvick, deputy director for safety in FDA's Division of Gastroenterology Products, in a statement.

The FDA did not have access to the raw data in the studies; it merely reviewed what was published. But, said the FDA, it accepted the results because the studies appear to be well designed. Even so, those studies had limitations, and there is still no understanding of why PPIs might lead to fractures.

—Alicia Ault

The full agency communication is located at www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm.