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 categoryan 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."

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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."

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

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

-Alicia Ault

The full agency communication is located at www.fda.gov/Drugs/DrugSafety/Postmar ketDrugSafetyInformation for Patients andProviders/ucm213206.htm.

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

Major Finding: The specificity of a new

screening approach developed for post-

Data Source: A single arm, prospective,

Disclosures: One of the study authors, Dr.

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.

cancer was 99.9%.

menopausal women at average risk for ovarian

multi-center study of 3,252 women aged 50-74.

Herbert A. Fritsche, disclosed that he received

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.

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

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

Fluid Retention

trogen 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.

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.

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, system lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these condition **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 manage of moderate to severe symptoms of vulvar and vaginal atrophy.

of moderate to severe symptoms of v **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_a levels (by column or by radioimmunoassay) or T_a levels by radioimmunoassay, T_a resin uptake is decreased, reflecting the elevated TBG. Free T_a and free T_a 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). proteins tray be incleased (aliquerising ethician substacts, applier (-anturypoin, beholiphasimi) Increased plasma HDL and HDL, cholesterol subfraction concentrations, reduced LDL cholestero 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.

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 write 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 Report	ing Treatment Em	ergent Adverse I	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	n				
Vasodilatation	5 (3.5)	4 (5.6)	7 (5.0)	1 (1.5)	

Table 1: Number (%) of Patients Reporting Treatment Emergent Adverse Events \geq 5 Percent Only Digestive System 4 (2.8) 2 (2.8) 10 (7.1) 1 (1.5) Nausea 5 (3.5) 3 (2.1) 3 (4.4) 5 (3.5) 5 (6.9) 6 (4.3) 4 (5.9) Arthralgia **Nervous System** 3 (4.2) 4 (2.9) 4 (5.9) Respiratory System 7 (5.0) Cough Increased 1 (1.4) 3 (4.4) Pharyngitis 3 (2.1) 2 (2.8) 7 (5.0) 3 (4.4) 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) n Leukorrhea 3 (2.1) 2 (2.8) 4 (2.9) 6 (8.8) 8 (5.6) 3 (4.2) 7 (5.0) 3 (4.4) Body system totals are not necessarily report two or more different adverse of the system. ım of the

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.

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, de

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 Crea

Metabolic Interactions

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 uteriable 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.

an oral contraceptive inadvertentity during early pregnancy.

Mursing 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

Geriatric Use

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 respo
to PREMARIN Vaginal Cream.
The Women's Health Initiative Study
In the Memory Is 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
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]. Industrial when to implicate to precede the second producted in women 65 to 79 years of age, it is unknown whether findings apply to younger postmenopausal women [see Clinical Studies (14.3) in full Prescribing Info

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.

Pfizer

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