laparoscopic hysterectomies. Overall, 1.5% had urgent clinic visits after their hysterectomy and discharge. Four percent visited the emergency department within 48 hours of the procedure, mainly for nausea or vomiting, urinary retention, or pain.

Of patients who underwent supracervical laparoscopic hysterectomy, 0.7% were readmitted within 48 hours, and 3.4% within 3 months. In those who underwent total laparoscopic hysterectomy, 0.4% were readmitted within 48 hours, and 4.1% within 3 months.

The two subgroups did not differ significantly in any outcomes.

S

Records from the hysterectomies showed a mean operating time of 157 minutes, a median estimated blood loss of 50 mL, and a mean uterine weight of 222 g. Hysterectomies were performed because of fibroids in 46% of patients, for menorrhagia in 27%, for pain in 15%, and for other reasons in 12%.

Patients in the current study had a median age of 45 years and a median body mass index of 28 kg/m^2 ; 35% had a BMI greater than 30. ■

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 induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. ould be 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.

pressma angivernoes reading 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_a and T_a serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are Setuit builte in a set in the initial range. We have a set of the 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.

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 postpost-hysterectomy with estrogen-alone therapy. For women known 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

or rubber should be considered.
Laboratory Tests
Serum folicile 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 and thrombin III activity;
Increased plateling and fibrinogen activity; increased plateling and activity.
Increased thronid-hindin niholilin (TBG) leading to increased circulating total thronome, as measured by

Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PB), T₄ levels (by column or by radioimmunoassay) or T₃ levels by radioimmunoassay, T₅ resin uptake is decreased, reflecting the elevated TBG. Free T₄ and free T₃ 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 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 In a 12-week, randomized, double-blind, placebo-controlled trial of PHEMARIN Vaginal Cream (PCU), 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; g PVC twice weekly), 68 women in the matching placebo treatment with PVC, including those subjects randomized at baseline to placebo. In this study, the most common adverse reactions \geq 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 \geq 5 Percent Only

	Ireatment				
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)	

Major Finding: Among 287 patients who underwent supracervical laparoscopic hysterectomy, only 0.7% were readmitted within 48 hours, and 3.4% within 3 months. Among 241 patients who underwent total laparoscopic hysterectomy, only 0.4% were readmitted within 48 hours, and 4.1% within 3 months.

Data Source: Retrospective case series of all women undergoing a laparoscopic hysterectomy for benign indications, performed by ob.gyn. generalists. Disclosures: None was reported.

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	n			
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)

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, vagini (including vaginal candidiasis), change in cervical secretion, cystitis-like syndrome, application site reactions of vulvovaginal discomfort, (including burning, irritation, and genital pruritus), endometrial hyperplasia, endometr 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

Increase or decrease in weight, glucose intolerance, edema, arthralgias, leg cramps, changes in libido, urticari anaphylactic reactions, exacerbation of asthma, increased triglycerides, hypersensitivity. Additional postmarketing adverse reactions have been reported in patients receiving other forms of hormone therap DRUG INTERACTIONS

No formal drug interaction studies have been conducted for PREMARIN Vaginal Cre Metabolic Interactions

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). In wird and in worsuldies have shown that estrogens are metaolized partially by cytochrome r420 3A4 (CH13A4). Therefore, inducers or inhibitors 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, itaconazole, 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 t little or no increased risk of birth defects in children born to women who have used estrogens and progestins an oral contraceptive inadvertently during early pregnancy.

an oral contraceptive inauvertenuty 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 PREMARI Vaginal Cream is administered to a nursing woman.

Pedi tric Use

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

Variation of the set o

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 exceeding internation, In the WHI exceeding internation, progestin substudy, there was a higher relative risk of nonfatal stroke and invasive breas 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, the 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 11/0

Pfizer

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Fortified OC **Raised Blood Folate Levels**

BY SHERRY BOSCHERT

FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

SAN FRANCISCO — A folate-fortified oral contraceptive significantly improved folate levels in red blood cells and plasma compared with a conventional oral contraceptive after 24 weeks, in a preliminary randomized, double-blind trial of 379 healthy U.S. women seeking contraception.

The study randomized 94 women to take the oral contraceptive Yaz (ethinyl estradiol 0.02 mg plus 3 mg drospirenone) and 285 women to take an experimental version of Yaz that also contained 0.451 mg levomefolate calcium, the calcium salt of L-5-methyltetrahydrofolate, the most prevalent form of dietary folate. During each of six treatment cycles, they got fortified Yaz or conventional Yaz for 24 days, followed by 4 days of levomefolate calcium alone in the fortified group or placebo in the control group.

Seventy women in the control group and 203 in the fortified group completed the 24 weeks of treatment, at which time average red blood cell folate levels were 1,406 nmol/L in the fortified group and 1,024 nmol/L in the control group. Plasma folate levels averaged 61 nmol/L in the fortified group and 41 nmol/L in the control group, Dr. Stephan Bart reported at the meeting.

The differences between groups were statistically significant, said Dr. Bart, a contract researcher at SNBL Clinical Pharmacology Center, Baltimore. Overall rates of adverse events were similar between groups.

The study did not restrict the use of additional folate-containing supplements, and U.S. women generally consume folate-fortified foods, emphasizing that a folate-fortified contraceptive could increase folate levels even in populations already exposed to sources of folate, he noted.

These results support the concept that folate-fortified oral contraceptives would improve the folate status of all women of childbearing potential," Dr. Bart said.

Among the women, aged 18-40 years, one or more adverse events were reported in 56% of the fortified group and 57% of the control group. Most adverse events were mild or moderate in intensity and consisted mainly of upper respiratory tract infections (10% of each group) or increases in low-density lipoprotein cholesterol (6% of the fortified group and 9% of the control group), Dr. Bart said.

Disclosures: Bayer Healthcare

Pharmaceuticals, which markets Yaz and is developing the folate-fortified version, funded the trial and Dr. Bart's travel to the meeting. His associates in the study all were employees of divisions of Bayer.