

POLICY & PRACTICE

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College Offers Advertising Advice

It is ethical for physicians to advertise their services, but they must be careful not to mislead the public or imply a lack of competence by their competition, according to an updated policy statement from the American College of Obstetricians and Gynecologists. It advises physicians to use caution when putting together advertisements because the public can easily be mislead. For example, potential patients might assume that any obstetrician advertising under the heading "infertility" has special training or certification in that area. Physicians should also be able to substantiate their claims if they use words like "top" or "pioneer." If a physician is voted a "top doctor" by magazine readers, that fact can be advertised. But if that designation was paid for, that must be disclosed in the ad as well, according to the ACOG policy. Also, doctors should shy away from advertising specific outcomes since treatment success often depends on patient factors. The policy, developed by the ACOG Committee of Ethics, was scheduled to be published in the November issue of Obstetrics and Gynecology.

Public Citizen Attacks Liability Caps

The medical liability reform law enacted in Texas in 2003 has failed to bring down medical costs or attract physicians to the state, according to an analysis by Public Citizen. The consumer-watchdog group said the law, which includes a \$250,000 cap on noneconomic damages, benefited malpractice insurance companies and physicians, who saw premiums and payouts decrease, but not the public. The report notes that Medicare spending per beneficiary in Texas has risen 13% faster than the national average and that diagnostic-testing expenses rose 25% more than the national average. Meanwhile, the increase in physicians per capita has slowed to less than half its rate in the years before the law was enacted. But Texas Medical Association President Dr. C. Bruce Malone said in an interview that the state has not boosted its physician population much because it's difficult to attract doctors to a poor state with a large population of uninsured people. Dr. Malone also said that liability reform has improved patients' access to care, especially in obstetrics. There are

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now many rural areas that have ob.gyns. for the first time, and more obstetricians are willing to take on high-risk pregnancies, he said.

Defending Planned Parenthood

House Democrats are standing up for Planned Parenthood, saying that the organization is being unfairly targeted for political reasons. In September, the Republican-controlled House Energy and Commerce subcommittee on oversight and investigations launched an inquiry into how the Planned Parenthood Federation and its affiliates handle federal funds. In a letter to the subcommittee's chairman, Rep. Cliff Stearns (R.-Fla.), top Democrats on the full committee criticized the investigation as an "unfair and unjustified assault." Rep. Henry Waxman (D.-Calif.) and Rep. Diana DeGette (D.-Colo.) wrote that the investigation was unnecessary because the Health and Human Services Inspector General and

state Medicaid programs routinely audit Planned Parenthood and report their findings to the public.

Millions Get Free Mammograms

More than 4 million women have received free mammograms this year as a benefit from the Affordable Care Act. The 2010 health-reform law allows Medicare beneficiaries to receive preventive services, including mammograms and cervical cancer screening, without paying a deductible or other cost. The benefit also includes a free annual wellness visit. The Department of Health

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 communication department toll-free at 1-800-934-5556.

WARNING: CARDIOVASCULAR DISORDERS, ENDOMETRIAL CANCER, BREAST CANCER and PROBABLE DEMENTIA ESTROGEN-ALONE THERAPY

ENDOMETRIAL CANCER

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 endometria hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, includirected or random endometrial sampling when indicated, should be undertaken to rule out malign in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [see Warnings and Precautions (5.3)].

Is 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

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 deme [see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3) in full prescribing information]. [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 treatmen 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 developi 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

JUAN INVIS AND DARE statment of Atrophic Vaginitis and Kraurosis Vulvae atment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Meno, CONTRAINDICATIONS

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

- PREMARIN Vaginal Cream therapy should not be used in women with any or the following conducts.

 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
- Known liver dysfunction or disease
- Known thrombophilic disorders 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.

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.

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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)

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 ¹ gee Clinical Studies (14.2) in the 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.

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.

Repart Cancer.

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) in full prescribing information].

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. 4mong women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.66, 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]*.

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 combinations, coses, or rotues 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 nCl 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

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. to 1,394 in Historical Continued worline to 10 79 years of age was randomized to daily CE (0.625 high or placebook. 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 nct 0.83-2.66). The absoluter isk 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].

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 nCl 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 nCl 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 given 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 reporte

and Human Services estimated that more than 20 million Medicare beneficiaries have received some type of preventive service this year, from cholesterol screening to bone-mass measurement.

Baby-Friendly Hospitals Sought

Officials at the Centers for Disease Control and Prevention are spending \$6 million over 3 years to help hospitals do a better job of supporting breastfeeding by new mothers. The goal is to get more U.S. hospitals to become "baby-friendly" facilities along the lines of a World Health Organization-UNICEF program that recognizes hospitals that follow science-based practices that increase breastfeeding rates. Currently, only about 5% of babies in the United States are born in "baby-friendly" hospitals, according to the CDC. The agency awarded its \$6 million to the National Initiative for Children's Healthcare Quality, which will work with hospitals to bring in experts in breastfeeding and quality improvement to develop system-level changes.

Panel: Patients' Needs Overlooked

Even though most doctors realize that

improving patient engagement can reduce costs and improve care, physicians still frequently overlook patients' needs and concerns, according to a report from the Institute of Medicine. For example, studies show that quality improves when providers listen carefully to patients and their families, according to the report based on an April workshop. However, other research has shown that physicians typically interrupt within 15 seconds of a patient beginning to raise concerns.

-Mary Ellen Schneider



Visual Ahnormalities

visual Autormanues

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 will estrogen in a continuous regimen have reported a lowered incidence of endometrial hyperplasia than wo 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

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 T4 and T3 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.

Angioedema

Exogenous estrogens may induce or exacerbate symptoms of angioedema, particularly in women with

hereditary angioedema. Exacerbation of Other Conditions

Extragent herapy 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.

or 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 increased factors II, VIII antigen, VIII antigen, VIII caugulant activity, IX, X, XII, VII-X complex, III-VII-X complex, beta-thromboglobulin; decreased elvels of antifactor Xa and antithrombin III. decreased antithrombin III act 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 me protein-bound iodine (PBI), T_c levels (by column or by radioimmunoassay) or T_c levels by radioimmuno resin uptake is decreased, reflecting the elevated TBG. Free T_c and free T_c concentrations are unaltered on thyroid replacement therapy may require higher doses of thyroid hormone. radioimmunoassay. T₃´ s are una**l**tered. Women

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.

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)]

• 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 wor 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 tull prescribing information].

Table 1: Number (%)	of Patients Report	ing Treatment En	nergent 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 Syste	m					

Vasodi l atation	5 (3.5)	4 (5.6)	7 (5.0)	1 (1.5)
Table 1: Number (%) o	f Patients Reporti	ng Treatment Em	ergent Adverse Ev	ents ≥ 5 Percent Only
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 Syste	m			
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 reactio are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

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 disea

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.

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.

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

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 WH! bestrogen-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].

placebo), there was a nignet relative new or substitution full prescribing information.

In the WHI estrogen plus progestin substudy, there was a higher relative risk of nonfatal stroke and invicancer in women greater than 65 years of age [see Clinical Studies (14.2) in full prescribing information in the work of the program of the pr

The Women's Health Initiative Memory Study
In 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].
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 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 W10413C022 ET01, Rev 05/10.

