Premarin® Vaginal Cream
(Conjugated Estrogens, 0.625 mg/g)

INDICATIONS AND CLINICAL USE

Premarin® Vaginal Cream is indicated in the treatment of atrophic vaginitis, dyspareunia, and kraurosis vulvae.

PREMARIN® VAGINAL CREAM HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS.

Premarin® Vaginal Cream should be prescribed with an appropriate dose of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma.

Geriatrics (>65 years of age): See above indications.

Pediatrics (<16 years of age): Premarin® Vaginal Cream is not indicated for use in children.

CONTRAINDICATIONS

Premarin® Vaginal Cream is contraindicated in the following conditions:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container.
- Liver dysfunction or disease as long as liver function tests have failed to return to normal.
- Known or suspected estrogen-dependent malignant neoplasia (e.g., endometrial cancer).
- Endometrial hyperplasia.
- Known, suspected, or past history of breast cancer.
- Undiagnosed abnormal genital bleeding.
- Known or suspected pregnancy (see **WARNINGS AND PRECAUTIONS**, **Special populations**, **Pregnant women**).
- Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis.
- Active or past history of arterial thromboembolic disease (e.g., stroke, myocardial infarction, coronary heart disease).
- Partial or complete loss of vision due to ophthalmic vascular disease.
- Known thrombophilic disorders (e.g., protein C, protein S or antithrombin deficiency); (prothrombin mutation or anticardiolipin antibodies).
- Migraine with or without aura.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial examined the health benefits and risks of oral combined *estrogen plus progestin* therapy (n = 16,608) and oral *estrogen-alone* therapy (n = 10,739) in post-menopausal women aged 50 to 79 years.

The *estrogen plus progestin* arm of the WHI trial (mean age 63.3 years) indicated an increased risk of *myocardial infarction* (MI), *stroke, invasive breast cancer, pulmonary emboli* and *deep vein thrombosis* in post-menopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day) for 5.2 years compared to those receiving placebo.

The *estrogen-alone* arm of the WHI trial (mean age 63.6 years) indicated an increased risk of *stroke* and *deep vein thrombosis* in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo.

Therefore, the following should be given serious consideration at the time of prescribing:

- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
- Estrogens with or without progestins should be prescribed at **the lowest effective dose** for the approved indication.
- Estrogens with or without progestins should be prescribed for the **shortest period possible** for the approved indication.

General

For the treatment of post-menopausal symptoms, hormone replacement therapy (HRT) should only be initiated for symptoms/conditions that are consistent with the indications (see **INDICATIONS AND CLINICAL USE**). In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risks.

Combined Estrogen and Progestin Therapy:

There are additional and/or increased risks that may be associated with the use of combination estrogen-plus-progestin therapy compared with using estrogen-alone regimens. These include an increased risk of myocardial infarction, pulmonary embolism, invasive breast cancer and ovarian cancer.

Systematic absorption may occur with the use of Premarin® Vaginal Cream. Warnings and precautions associated with oral Premarin® treatment should be taken into account.

Latex Condoms

NOTE: Preliminary studies conducted by the Health Products and Food Branch have demonstrated that Premarin® Vaginal Cream may react with the latex rubber of certain mechanical barrier devices used for prevention of sexually transmitted

diseases and pregnancy (diaphragms and condoms). In additional studies, Premarin® Vaginal Cream has been shown 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.

Carcinogenesis and Mutagenesis

Breast cancer

Available epidemiological data indicate that the use of combined *estrogen plus progestin* by post-menopausal women is associated with an increased risk of invasive breast cancer.

In the *estrogen plus progestin* arm of the WHI trial, among 10,000 women over a one-year period, there were:

- 8 more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo).

The WHI study also reported that the invasive breast cancers diagnosed in the *estrogen plus progestin* group were similar in histology but were larger (mean [SD], 1.7 cm [1.1] vs. 1.5 cm [0.9], respectively; P = 0.04) and were at a more advanced stage compared with those diagnosed in the placebo group. The percentage of women with abnormal mammograms (recommendations for short-interval follow-up, a suspicious abnormality, or highly suggestive of malignancy) was significantly higher in the *estrogen plus progestin* group versus the placebo group. This difference appeared at year one and persisted in each year thereafter.

In the *estrogen-alone* arm of the WHI trial, there was no statistically significant difference in the rate of invasive breast cancer in hysterectomized women treated with conjugated equine estrogens versus women treated with placebo.

It is recommended that estrogens not be given to women with existing breast cancer or those with a previous history of the disease (see **CONTRAINDICATIONS**).

There is a need for caution in prescribing estrogens for women with known risk factors associated with the development of breast cancer, such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (abnormal mammograms and/or atypical hyperplasia at breast biopsy).

Other known risk factors for the development of breast cancer such as nulliparity, obesity, early menarche, late age at first full-term pregnancy and at menopause should also be evaluated.

It is recommended that women undergo mammography prior to the start of HRT treatment and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.

The overall benefits and possible risks of hormone replacement therapy should be

fully considered and discussed with patients. It is important that the modest increased risk of being diagnosed with breast cancer after 4 years of treatment with combined estrogen plus progestin HRT (as reported in the results of the WHI trial) be discussed with the patient and weighed against its known benefits.

Instructions for regular self-examination of the breasts should be included in this counselling.

Endometrial hyperplasia and endometrial carcinoma

The use of unopposed estrogens has been associated with an increased risk of endometrial hyperplasia/carcinoma. Estrogen should be prescribed with an appropriate dosage of a progestin for women with intact uteri or hysterectomized women with a history of residual endometriosis in order to prevent endometrial hyperplasia/carcinoma (see **WARNINGS AND PRECAUTIONS**, ***Endometriosis***).

The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold or greater than in non-users and appears to be dependent on duration of treatment and on estrogen dose. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five years or more, and this risk has been shown to persist for at least 8 to 15 years after ERT is discontinued. Adding a progestin to post-menopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer (see **WARNINGS AND PRECAUTIONS**, **General**).

Clinical surveillance of all women taking combined estrogen plus progestin HRT is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Ovarian cancer

In some epidemiologic studies, the use of estrogen therapy, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer.

Cardiovascular

Cardiovascular risk

ERT has been reported to increase the risk of stroke and deep venous thrombosis (DVT).

Risk factors for cardiovascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) should be managed appropriately.

The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of *estrogen plus progestin* is associated with an increased risk of coronary heart disease (CHD) in post-menopausal women. The results of the WHI trial indicate that the use of *estrogen-alone* and *estrogen plus progestin* is associated with an increased risk of

stroke in post-menopausal women.

Patients who are at risk of developing migraines with aura may be at risk of ischemic stroke and should be kept under careful observation.

Should a stroke occur or be suspected, Premarin® Vaginal Cream should be discontinued immediately.

WHI trial findings

In the combined *estrogen plus progestin* arm of the WHI trial, among 10,000 women over a one-year period, there were:

- 8 more cases of stroke (29 on combined HRT versus 21 on placebo).
- 7 more cases of CHD (37 on combined HRT versus 30 on placebo).

In the *estrogen-alone* arm of the WHI trial of women with prior hysterectomy, among 10,000 women over a one-year period, there were/was:

- 12 more cases of stroke (44 on *estrogen-alone* therapy versus 32 on placebo)
- no statistically significant difference in the rate of CHD.

HERS and HERS II findings

In the Heart and Estrogen/progestin Replacement Study (HERS) of post-menopausal women with documented heart disease (n = 2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg oral medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit. Specifically, during an average follow-up of 4.1 years, treatment with CEE plus MPA did not reduce the overall rate of CHD events in post-menopausal women with established coronary heart disease. There were more CHD events in the hormone-treated group than in the placebo group in year 1, but not during the subsequent years.

From the original HERS trial, 2321 women consented to participate in an open label extension of HERS known as HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD.

Blood pressure

Women using hormone replacement therapy sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be investigated and HRT may have to be discontinued.

Endocrine and Metabolism

Glucose and lipid metabolism

A worsening of glucose tolerance and lipid metabolism has been observed in a significant percentage of peri- and post-menopausal patients. Therefore, diabetic patients, or those with a predisposition to diabetes, should be observed closely to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride blood levels.

Women with familial hyperlipidemias need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started.

Caution should be exercised in patients with pre-existing hypertriglyceridemia since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this population.

Heme metabolism

Women with porphyria need special surveillance.

Estrogens should be used with caution in individuals with pre-existing severe hypocalcemia.

Calcium and phosphorus metabolism

Because the prolonged use of estrogens influences the metabolism of calcium and phosphorus, estrogens should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients who require thyroid hormone replacement therapy and who are also taking estrogen 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 (see ***Drug-laboratory Test Interactions***).

Genitourinary

Endometriosis

Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use. 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.

Uterine Leiomyomata

Pre-existing uterine leiomyomata may increase in size during estrogen use. Growth, pain or tenderness of uterine leiomyomata requires discontinuation of medication and appropriate investigation.

Vaginal bleeding

Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt appropriate diagnostic measures to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.

Hematologic

Venous thromboembolism

Available epidemiological data indicate that use of estrogen with or without progestin by post-menopausal women is associated with an increased risk of developing venous thromboembolism (VTE).

In the oral *estrogen plus progestin* arm of the WHI trial, among 10,000 women on combined HRT over a one-year period, there were 18 more cases of venous thromboembolism, including 8 more cases of pulmonary embolism.

In the oral *estrogen-alone* arm of the WHI trial, among 10,000 women on estrogen therapy over a one-year period, there were 7 more cases of venous thromboembolism, although there was no statistically significant difference in the rate of pulmonary embolism.

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index >30 kg/m^2) and systemic lupus erythematosus. The risk of VTE also increases with age and smoking.

The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or trauma. In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. Also, patients with varicose veins should be closely supervised. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism, and pulmonary embolism). If these occur or are suspected, Premarin® Vaginal Cream should be discontinued immediately, given the risks of long-term disability or fatality.

If feasible, Premarin® Vaginal Cream should be discontinued at least 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Hepatic/Biliary/Pancreatic

Liver disorders

Patients who have previously had liver disorders, such as liver adenoma should be closely supervised as this condition may recur or be aggravated during treatment with

Premarin® Vaginal Cream.

Gallbladder diseases

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

Hepatic hemangiomas

Particular caution is indicated in women with hepatic hemangiomas, as HRT may cause an exacerbation of this condition.

Jaundice

Caution is advised in patients with a history of liver and/or biliary disorders. If cholestatic jaundice develops during treatment, the treatment should be discontinued and appropriate investigations carried out. Estrogens may be poorly metabolized in patients with impaired liver functions.

Liver function tests

Liver function tests should be done periodically in subjects who are suspected of having hepatic disease. For information on endocrine and liver function tests, see ***Monitoring and Laboratory Tests***.

Immune

Systemic lupus erythematosus

Particular caution is indicated in women with systemic lupus erythematosus, as HRT may cause an exacerbation of this condition.

Angioedema

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

Neurologic

Cerebrovascular insufficiency

Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis, or loss of consciousness should discontinue medication.

Patients with a previous history of classical migraine and who develop a recurrence or worsening of migraine symptoms should be reevaluated.

Ophthalmologic: If visual abnormalities develop: Discontinue Premarin® Vaginal Cream 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, Premarin® Vaginal Cream should be withdrawn. Retinal vascular thrombosis has been reported in patients receiving estrogens with or without progestins (see **WARNINGS AND PRECAUTIONS**, **Hematologic**, ***Venous thromboembolism***).

Dementia

Available epidemiological data indicate that the use of combined *estrogen plus progestin* in women age 65 and over may increase the risk of developing probable dementia.

The Women's Health Initiative Memory Study (WHIMS), a clinical substudy of the WHI, was designed to assess whether post-menopausal hormone replacement therapy (oral *estrogen plus progestin* or oral *estrogen-alone*) reduces the risk of dementia in women aged 65 and over (age range 65-79 years) and free of dementia at baseline.

It is unknown whether these findings apply to younger post-menopausal women (see **Special Populations, Geriatrics**).

In the *estrogen plus progestin* arm of the WHIMS (n = 4532), women with intact uteri were treated with daily 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) or placebo for an average of 4.05 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 23 more cases of probable dementia (45 on combined HRT versus 22 on placebo).

In the *estrogen-alone* arm of the WHIMS (n = 2947), women with prior hysterectomy were treated with daily 0.625 mg CEE or placebo for an average of 5.21 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 12 more cases of probable dementia (37 on *estrogen-alone* versus 25 on placebo), although this difference did not reach statistical significance.

When data from the *estrogen plus progestin* arm of the WHIMS and the *estrogen-alone* arm of the WHIMS were combined, as per the original WHIMS protocol, in 10,000 women over a one-year period, there were:

- 18 more cases of probable dementia (41 on *estrogen plus progestin* or *estrogen-alone* versus 23 on placebo).

Epilepsy

Particular caution is indicated in women with epilepsy, as HRT may cause an exacerbation of this condition.

Ear/Nose/Throat

Otosclerosis

Estrogens should be used with caution in patients with otosclerosis.

Psychiatric

Depression

Patients who are taking progestogens and have a history of depression should be observed. If the depression occurs to a serious degree, the drug should be discontinued.

Renal

Fluid retention

Estrogens may cause fluid retention.

Therefore, particular caution is indicated in cardiac, renal dysfunction, or asthma. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be reassessed based on the individual case.

Special Populations

Pregnant Women: Premarin® Vaginal Cream is contraindicated during pregnancy (see **CONTRAINDICATIONS**). If pregnancy occurs during medication with PREMARIN treatment should be withdrawn immediately.

Nursing Women: Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of breast milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving the drug. Where an assessment of the risk to benefit ratio suggests the use of this product in nursing women is unfavorable, formula feeding should be substituted for breast feeding.

Pediatrics (<16 years of age): Premarin® Vaginal Cream is not indicated for use in children. Safety and effectiveness in pediatric population have not been established. Estrogen treatment of prepubertal girls induces premature breast development and vaginal cornification, and may induce uterine bleeding.

Since large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, hormonal therapy should not be started before epiphyseal closure has occurred in order not to compromise final growth.

Geriatrics (>65 years of age): The estrogen-alone substudy of the Women's Health Initiative (WHI) reported an increased risk of stroke compared with placebo in post-menopausal women 65 years of age or older (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular**, and **CLINICAL TRIALS**).

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.

Information for Patients
No studies on the effect of ability to drive or use machines have been performed.

Monitoring and Laboratory Tests

Before Premarin® Vaginal Cream is administered, the patient should have a complete physical examination including blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. Endometrial biopsy should be done only when indicated. Baseline tests should include mammography, measurements of blood glucose, calcium, triglycerides and cholesterol, and liver function tests. Before starting treatment, pregnancy should be excluded. Periodic check-ups and careful benefit/risk evaluations should be undertaken in women treated with ERT/HRT therapy. The first follow-up examination should be done within three to six months of initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals of at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the physician.

Mammography examinations should be scheduled based on patient age, risk factors and prior mammogram results.

The importance of regular self-examination of the breasts should be discussed with the patient.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

See **Warnings/Precautions** regarding potential induction of malignant neoplasia and other adverse effects similar to those observed with oral contraceptives.

The following additional adverse reactions have been reported with conjugated estrogens vaginal cream or are undesirable effects associated with ET/HT:

Blood and lymphatic system disorders

Altered coagulation tests (see **WARNINGS AND PRECAUTIONS**, **Drug-laboratory Tests Interactions**).

Cardiac disorders

Palpitations; increase in blood pressure (see **WARNINGS AND PRECAUTIONS**); coronary thrombosis, pulmonary embolism, venous thrombosis, myocardial infarction.

Endocrine disorders

Increased blood sugar levels; decreased glucose tolerance, precocious puberty.

Eye disorders

Neuro-ocular lesions (e.g., retinal vascular thrombosis, optic neuritis); visual disturbances; steepening of the corneal curvature; intolerance to contact lenses.

Gastrointestinal disorders

Nausea; vomiting; abdominal discomfort (cramps, pressure, pain, bloating), pancreatitis; ischemic colitis.

General disorders and administration site conditions

Fatigue; changes in appetite; changes in body weight; changes in libido, aggravation of porphyria, hypocalcemia (in patients with pre-existing conditions of hypocalcemia), angioedema, hypersensitivity, anaphylactic/anaphylactoid reactions, increased triglycerides.

Hepatobiliary disorders

Gallbladder disorder; cholestatic jaundice, asymptomatic impaired liver function.

Musculoskeletal and connective tissue disorders

Musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur, arthralgia, leg cramps.

Neoplasms, benign

Fibrocystic breast changes; enlargement of hepatic hemangiomas; growth potentiation of benign meningioma.

Nervous system disorders

Aggravation of migraine episodes; headaches; migraines, dizziness; cerebrovascular accident/stroke; exacerbation of chorea, neuritis.

Psychiatric disorders

Mental depression; nervousness; irritability, mood disturbances, dementia.

Renal and urinary disorders

Cystitis-like syndrome; dysuria; sodium retention; edema.

Reproductive system and breast disorders

Abnormal uterine bleeding; change in menstrual flow; dysmenorrhea/pelvic pain; vaginal itching/discharge; dyspareunia; endometrial hyperplasia; pre-menstrual-like syndrome; reactivation of endometriosis; changes in cervical erosion and amount of cervical secretion; breast swelling and tenderness, galactorrhea, breast discharge, amenorrhea, increase in size of uterine leiomyomata, vaginitis, application site reactions of vulvovaginal discomfort including burning, irritation and genital pruritus,

vaginal candidiasis; leukorrhea.

Skin and subcutaneous tissue disorders

Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; haemorrhagic eruption; loss of scalp hair; hirsutism and acne, allergic reactions and rashes, generalized rash, uticaria, pigmentation of the skin, pruritus.

Vascular disorders

Isolated cases of: thrombophlebitis; thromboembolic disorders.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Low Dose Regimen

In a 12-week, randomized, double-blind, placebo-controlled trial of conjugated estrogens vaginal cream [Premarin® Vaginal Cream (PVC)], a total of 423 post-menopausal 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, there were no statistically significant differences in adverse reactions between PVC and placebo. The most common adverse drug reactions ≥1% are shown below (Table 1).

Table 1: Number (%) of Patients Reporting Treatment Emergent Adverse Drug Reactions ≥1%

	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 (%)
BODY AS A WHOLE				
Abdominal Pain	11 (7.7)	2 (2.8)	9 (6.4)	6 (8.8)
CARDIOVASCULAR SYSTEM				
Hypertension	2 (1.4)	2 (2.8)	5 (3.6)	0
Migraine	2 (1.4)	0	0	2 (2.9)
DIGESTIVE SYSTEM				
Abdominal Distension	2 (1.4)	1 (1.4)	2 (1.4)	1 (1.5)
Nausea	5 (3.5)	4 (5.6)	3 (2.1)	4 (5.9)

Table 1: Number (%) of Patients Reporting Treatment Emergent Adverse Drug Reactions ≥1%				
	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 (%)
Vomiting	3 (2.1)	2 (2.8)	3 (2.1)	3 (4.4)
METABOLIC AND NUTRITIONAL				
Peripheral Edema	2 (1.4)	0	0	0
Weight Gain	3 (2.1)	1 (1.4)	1 (0.7)	0
MUSCULOSKELETAL SYSTEM				
Arthralgia	4 (2.8)	5 (6.9)	5 (3.6)	4 (5.9)
SKIN AND APPENDAGES				
Pruritus	3 (2.1)	1 (1.4)	5 (3.6)	0
Rash	3 (2.1)	1 (1.4)	5 (3.6)	0
UROGENITAL SYSTEM				
Breast Pain	8 (5.6)	2 (2.8)	4 (2.9)	0
Cystitis	1 (0.7)	1 (1.4)	2 (1.4)	1 (1.5)
Leukorrhea	3 (2.1)	2 (2.8)	4 (2.9)	6 (8.8)
Metrorrhagia	3 (2.1)	2 (2.8)	0	1 (1.5)
Vaginal Hemorrhage	1 (0.7)	1 (1.4)	2 (1.4)	2 (2.9)
Vaginitis	8 (5.6)	3 (4.2)	7 (5.0)	3 (4.4)
Vuluovaginitis	0	1 (1.4)	2 (1.4)	0
a. Body system totals for the No. of Patients 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.				

Other Clinical Trial Adverse Drug Reactions (<1%)

The following adverse events were reported at an incidence of <1% for Premarin® Vaginal Cream regardless of drug relationship.

Body as a Whole: Carcinoma; Chills; Cyst; Fever; Injection Site Pain

Cardiovascular System: Cardiovascular Physical; Hemorrhage; Palpitation; Tachycardia

Digestive System: Cheilitis; Cholecystitis; Cholelithiasis; Colitis; Eructation; Esophagitis; Gastritis; Gingivitis; Increased Appetite; Oral Moniliasis; Periodontal Abscess; Tenesmus

Metabolic and Nutritional: Hyperglycemia; Hyperlipemia

Musculoskeletal System: Bone Disorder; Muscle Spasms; Musculoskeletal Stiffness

Nervous System: Agitation; Attention Deficit/Hyperactivity; Confusion; Hostility; Memory Impairment

Respiratory System: Pleural Disorder; Sputum Increased

Skin and Appendages: Alopecia; Hair Disorder; Herpes Simplex; Herpes Zoster; Lichenoid Dermatitis; Night Sweats; Sunburn; Urticaria

Special Senses: Dry Eyes; Ear Disorder; Eye Pain; Lacrimation Disorder

Urogenital System: Breast Disorder; Endometrial Disorder; Genital Edema; Hematuria; Urethral Pain; Urinary Incontinence; Urine Abnormality; Uterine Fibroids Enlargement

If adverse symptoms persist, the prescription of HRT should be re-considered.

Post-marketing Adverse Drug Reactions

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 post-marketing adverse reactions have been reported in patients receiving other forms of hormone therapy.

DRUG INTERACTIONS

No formal drug interactions studies have been conducted in Premarin® Vaginal Cream.

Overview

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, phenytoin, carbamazepine, rifampicin, and dexamethasone 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 cimetidine, erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice, may increase plasma concentrations of estrogens and may result in side effects.

Drug-drug Interactions

No formal drug-drug interactions studies with Premarin® Vaginal Cream have been conducted (see **Drug Interactions** – Overview).

Drug-food Interactions

No formal drug-food interactions studies with Premarin® Vaginal Cream have been conducted (see **Drug Interactions** – Overview).

CYP3A4 inhibitors such as grapefruit juice may increase plasma concentrations of 17ß-estradiol and may result in side effects.

Drug-herb Interactions

It was found that some herbal products (e.g., St. John’s Wort) which are available as over-the-counter (OTC) products might interfere with steroid metabolism and therefore alter the efficacy and safety of estrogen/progestin products.

Physicians and other health care providers should be made aware of other non-prescription products concomitantly used by the patient, including herbal and natural products obtained from the widely spread health stores.

Drug-laboratory Test Interactions

There are no studies investigating drug-laboratory test interactions with Premarin® Vaginal Cream.

The results of certain endocrine and liver function tests may be affected by estrogen-containing products:

- increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity, increased coagulation factors VII, VIII, IX, X; increased norepinephrine-induced platelet aggregability; decreased antithrombin III;

- impaired glucose tolerance;

- increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentrations, increased serum triglycerides and phospholipids concentration.

- increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone (T4), as measured by column or radioimmunoassay; T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

- other binding proteins may be elevated in serum i.e., corticosteroid binding globulin (CBG), sex-hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively, free or biologically active hormone concentrations are unchanged;

- the response to metyrapone may be reduced.

- the pathologist should be informed that the patient is receiving hormone replacement therapy (HRT) when relevant specimens are submitted.

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for two to four weeks.

Drug-lifestyle interactions
Acute alcohol ingestion during HRT may lead to elevations in circulating estradiol levels.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Premarin® Vaginal Cream alone, or in combination with progestins therapy, should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as clinical appropriate to determine if treatment is still necessary (see boxed Warnings and Precautions). For women who have intact uteri, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding. In the absence of comparable data, the risks of HRT should be assumed to be similar for all estrogens and estrogen/progestin combinations.

Hormone replacement therapy (HRT) involving either estrogen alone or estrogen plus progestin combined therapy should only be continued as the benefits outweigh the risks for the individual.

Recommended Dose and Dosage Adjustment

Premarin® Vaginal Cream should be administered cyclically for short-term use only for the treatment of atrophic vaginitis, dyspareunia or kraurosis vulvae.

Premarin® Vaginal Cream should be instituted at the lowest effective dosage, and the need for continued estrogen therapy should be re-evaluated regularly.

For maintenance therapy, one should always use the lowest dose that still proves effective. The requirement for hormone replacement therapy for menopausal symptoms should be reassessed periodically.

In some cases, hysterectomized women with a history of endometriosis may need a progestin, see **WARNINGS AND PRECAUTIONS, Endometriosis**.

Dosage Range

The lowest dose that will control symptoms should be chosen.

Low Dose

Premarin® Vaginal Cream (0.5 g) is administered intravaginally or topically twice-weekly (for example, Monday and Thursday).

Maximum Recommended Dose

Premarin® Vaginal Cream is administered intravaginally or topically in a cyclic regimen (daily for 21 days and then off for 7 days). Generally, women should be started at the 0.5 g daily dosage strength. Dosage adjustments (0.5 to 2 g) may be made based on individual response.

Appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

Instructions for Use of Applicator:

1. Remove cap.
2. Screw nozzle end of applicator onto the tube.
3. Gently squeeze tube to force sufficient cream into the barrel to provide the prescribed dose.
4. Unscrew applicator from tube.
5. Place the applicator into the vaginal opening.
6. To release medication, press plunger downward.

To Cleanse: Pull plunger out from barrel. Wash with mild soap and warm water. DO NOT BOIL.

Missed Dose

If a patient misses a dose, it should be taken as soon as possible. If it is close to the patient's next scheduled dose, the missed dose should be skipped, and the patient should continue with her normal schedule. The patient should not take two doses at the same time.

Administration

Vaginal

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

OVERDOSAGE

Symptoms of overdose:

Numerous reports of ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects.

Overdosage with estrogen may cause nausea, breast discomfort, fluid retention, bloating, or vaginal bleeding in women.

Treatment of overdose

There is no specific antidote and further treatment if necessary should be symptomatic.

For management of a suspected drug overdose, contact your doctor.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

from tissue to tissue. Estrogen receptors have been identified in various tissues including the wall of blood vessels, in tissues of the reproductive tract, breast, brain, liver, and bone of women. Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these gonadotropins seen in post-menopausal women.

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sex characteristics. By a direct action, they cause growth and development of the uterus, fallopian tubes, and vagina. With other hormones, such as pituitary hormones and progesterone, they cause enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat. Estrogens are intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy, and affect the release of pituitary gonadotropins. Indirectly, they also contribute to the shaping of the skeleton, maintenance of tone and elasticity through the increase of collagen production in the supportive tissues of the heart, skin and urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, growth of axillary and pubic hair, and pigmentation of the nipples and genitals. Decline of ovarian estrogenic and progestogenic activity at the end of the menstrual cycle can result in menstruation, although the cessation of progesterone secretion is the most important factor in the mature ovulatory cycle. However, in the preovulatory or anovulatory cycle, estrogen is the primary determinant in the onset of menstruation.

Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level.

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

Circulating estrogens modulate pituitary gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogen therapy acts to reduce elevated levels of these hormones seen in post-menopausal women.

Estrogen drug products act by regulating the transcription of a limited number of genes. They may act directly at the cell's surface via non-"estrogen receptor" mechanism or directly with the estrogen receptor inside the cell. Estrogens diffuse through cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein which is found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, which enhance the transcription of adjacent genes and in turn lead to the observed effects.

Estrogens used in therapy are also well absorbed through the skin and mucous membranes. When applied for a local action, absorption is usually sufficient to cause systemic effects. When conjugated with aryl and alkyl groups for parenteral administration, the rate of absorption of oily preparations is slowed with a prolonged duration of action, such that a single intramuscular injection of estradiol valerate or estradiol cypionate is absorbed over several weeks.

Pharmacodynamics

Currently, there are no pharmacodynamic data known for conjugated estrogens (CE) alone.

Conjugated estrogens used in therapy are soluble in water and are well absorbed through the skin, mucous membranes, and gastrointestinal tract after release from the drug formulation.

Effects on vasomotor symptoms associated with estrogen deficiency

Hot flushes, feelings of intense heat over the upper trunk and face, with flushing of the skin and sweating occur in approximately 80% of women as a result of the decrease in ovarian hormones. These vasomotor symptoms are seen in women whether menopause is surgically induced or spontaneous. However, hot flushes may be more severe in women who undergo surgical menopause. Hot flushes can begin before the cessation of menses.

Pharmacokinetics

Absorption

Conjugated estrogens are soluble in water and are well absorbed through the skin, mucous membranes, and the gastrointestinal tract after release from the drug formulation.

Distribution

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

Metabolism

Metabolic conversion of estrogens occurs primarily in the liver (first pass effect), but also at local target tissue sites. Complex metabolic processes result in a dynamic equilibrium of circulating conjugated and unconjugated estrogenic forms which are continually interconverted, especially between estrone and estradiol and between esterified and non-esterified forms.

Estrogen drug products administered by non-oral routes, while not subject to true “first-pass” metabolism, do undergo significant hepatic uptake, metabolism, and

enterohepatic recycling. Metabolism and inactivation occur primarily in the liver. Some estrogens are excreted into the bile; however, they are re-absorbed from the intestine and returned to the liver through the portal venous system. Water-soluble estrogen conjugates are strongly acidic and are ionized in body fluids, which favour excretion through the kidneys since tubular re-absorption is minimal.

When given orally, naturally-occurring estrogens and their esters are extensively metabolized (first pass effect) and circulate primarily as estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogenic species. This results in limited oral potency. By contrast, synthetic estrogens, such as ethinyl estradiol and the non-steroidal estrogens, are degraded very slowly in the liver and other tissues, which results in their high intrinsic potency.

Excretion

A certain proportion of the estrogen is excreted into the bile, then reabsorbed from the intestine and returned to the liver through the portal venous system. During this enterohepatic recirculation, estrogens are desulfated and resulfated and undergo degradation through conversion to less active estrogens (estriol and other estrogens), oxidation to non-estrogenic substances (catecholestrogens, which interact with catecholamine metabolism, especially in the central nervous system), and conjugation with glucuronic acids (which are then rapidly excreted in the urine).

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

Special Populations and Conditions

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

STORAGE AND STABILITY

Please refer to outer carton for storage condition.

SPECIAL HANDLING INSTRUCTIONS

None required.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PREMARIN® Vaginal Cream is available in tubes of 14 g, each gram containing 0.625 mg of conjugated estrogens. Each tube is accompanied with a calibrated plastic applicator.

Non-Medicinal Ingredients:	Cetyl Alcohol, Cetyl Esters Wax, Glycerin, Glyceryl Monostearate, Methyl Stearate, Mineral Oil, Phenylethyl Alcohol, Propylene Glycol Monostearate, Sodium Lauryl Sulfate, Water Purified, White Wax.

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Hong Kong