Conjugated Estrogen Vaginal Cream

Premarin®Vaginal Cream

1 GENERIC NAME

Conjugated Estrogen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of vaginal cream contains 0.625 mg conjugated estrogen.

List of Excipients

Cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, purified water, nitrogen and mineral oil.

3 DOSAGE FORM AND STRENGTH

Dosage Form: Vaginal cream

Strength: 0.625mg

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Conjugated estrogen vaginal cream is indicated in the treatment of atrophic vaginitis, dyspareunia and kraurosis vulvae (associated with the menopause).

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4.2 Posology and Method of Administration

If an estrogen is prescribed for a post-menopausal woman with a uterus, the addition of a progestin may be appropriate (see section, **4.4 Special Warnings and Special Precautions for Use-Malignant neoplasms**). In some cases, hysterectomized women with a history of endometriosis may need a progestin (see section, **4.4 Special Warnings and Special Precautions for Use-Exacerbation of other conditions**).

In a 52-week trial using Conjugated estrogen vaginal cream alone (in the absence of any progestin), 0.5 g twice weekly or 3 weeks on and 1 week off, there was no evidence of endometrial hyperplasia or endometrial carcinoma.

Dosage adjustment may be made based on individual patient response.

Use of Conjugated Estrogen Vaginal Cream, alone or in combination with a progestin, should be limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as cyclically appropriate (for e.g., 3 months to 6 months intervals) to determine if treatment is still necessary. For women with a uterus, 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.

Given cyclically for short-term use only:
For treatment of atrophic vaginitis, dyspareunia and kraurosis vulvae. The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible. Administration should be cyclic (e.g., 3 weeks on and 1 week off).

Usual Dosage Range:
½ to 2 g daily, intravaginally, depending on the severity of the condition.

Instructions for Use of Gentle Measure™ Applicator:
1. Remove cap from tube.
2. Screw nozzle end of applicator onto tube.
3. Gently squeeze tube from the bottom to force sufficient cream into the barrel to provide the prescribed dose. Use the marked stopping points on the applicator as a guideline to measure the correct dose.
4. Unscrew applicator from tube.
5. Lie on back with knees drawn up. To deliver medication, gently insert applicator deeply into vagina and press plunger downward to its original position.

To Cleanse: Pull plunger to remove it from barrel. Wash with mild soap and warm water.
DO NOT BOIL OR USE HOT WATER.

Use in the Elderly
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 section, **4.4 Special Warnings and Special Precautions for Use-Cardiovascular risk** and section, **5.1 Pharmacodynamic Properties-Clinical Efficacy**).

A substudy of the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI conducted in women aged 65-79, reported an increased risk of developing probable dementia when compared with placebo (see section, **4.4 Special Warnings and Special Precautions for Use-Dementia** and section, **5.1 Pharmacodynamic Properties-Clinical Efficacy**).

Use in Children
Clinical studies have not been conducted in the pediatric population.

Although estrogen replacement therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay, safety and effectiveness in pediatric patients have not otherwise been established. Estrogen treatment of pre-pubertal girls also 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.

Conjugated estrogen vaginal cream is not indicated in children.

4.3 Contraindications

Premarin vaginal cream is contraindicated in the following conditions:

1. Patients who are hypersensitive to this drug or to any ingredient in the formulation
2. Liver dysfunction or disease as long as liver function tests have failed to return to normal.
3. Known or suspected pregnancy (see section, **4.6 Fertility, Pregnancy and Lactation**).
4. Undiagnosed abnormal uterine bleeding.
5. Known, suspected or past breast cancer.
6. Known or suspected estrogen dependent malignant neoplasia (e.g., endometrial cancer)
7. Endometrial hyperplasia.
8. Active or history of arterial thromboembolic disease. (e.g., stroke, myocardial infarction) or venous thromboembolism (such as deep venous thrombosis, pulmonary embolism).
9. Active or chronic liver dysfunction or disease.

10. Partial or complete loss of vision due to ophthalmic vascular disease.
11. Known thrombophilic disorders (e.g., protein C, protein S OR antithrombin deficiency); prothrombin mutation or anticardiolipin antibodies).
12. Migraine with or without aura.

4.4 Special Warnings and Precautions for Use

SPECIAL WARNINGS

General
Systemic absorption may occur with the use of Conjugated estrogen vaginal cream. Warnings and precautions associated with oral Conjugated estrogen treatment should be taken into account.

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia.

The estrogen plus progestin substudy of WHI reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, ovarian cancer and DVT in post-menopausal women (50 to 79 years of age) during 5.6 years of treatment with daily Conjugated estrogen 0.625 mg combined with medroxyprogesterone acetate (MPA 2.5 mg), relative to placebo.

Cardiovascular risk
ERT has been reported to increase the risk of stroke and deep venous thrombosis (DVT). Patients who have risk factors for thrombotic disorders should be kept under careful observation.
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 postmenopausal 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 postmenopausal 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.

Stroke
In the estrogen-alone substudy of the WHI, a statistically significant increased risk of stroke was reported in women receiving estrogen alone compared to women receiving placebo (45 vs. 33 per 10,000 person-years). The increase in risk was observed during year one and persisted. Should a stroke occur or be suspected, estrogens should be discontinued immediately (see section **5.1**, **Pharmacodynamic Properties-Clinical Efficacy**).

Venous thromboembolism
In the estrogen-alone substudy of WHI, the increased risk of deep venous thrombosis (DVT) was reported to be statistically significant (23 vs. 15 per 10,000 person-years). The risk of pulmonary embolism (PE) was reported to be increased, although it did not reach statistical significance. The increase in VTE (DVT and PE) risk was demonstrated during the first two years (30 vs. 22 per 10,000 person-years). Should a VTE occur or be suspected, estrogens should be discontinued immediately (see section, **5.1 Pharmacodynamic Properties-Clinical Efficacy**).

If feasible, estrogens should be discontinued at least four to six weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Malignant neoplasms

Endometrial cancer
The use of unopposed estrogens in women with an intact-uterus has been associated with an increased risk of endometrial cancer. (see section, **4.4 Special Warnings and Special Precautions for Use-Exacerbation of other conditions** and section **5.1 Pharmacodynamic Properties-Clinical Efficacy**).

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. The greatest risk appears 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 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 section, **4.4 Special Warnings and Special Precautions for Use-General**).

Clinical surveillance of all women taking estrogen or estrogen-plus-progestin combinations 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 uterine bleeding.

Breast cancer
Studies involving the use of estrogens by post-menopausal women have reported inconsistent results on the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) (see section, **5.1 Pharmacodynamic Properties-Clinical Efficacy**). In the estrogen-alone substudy of WHI, after an average of 7.1 years of follow-up, Conjugated estrogen (0.625 mg daily) was not associated with an increased risk of invasive breast cancer.

Some observational studies have reported an increased risk of breast cancer for estrogen-alone therapy after several years of use. The risk increased with duration of use, and appeared to return to baseline within approximately 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping).

The use of estrogen has been reported to result in an increase in abnormal mammograms requiring further evaluation.

Ovarian cancer
In some epidemiologic studies, the use of estrogen-only products, has been associated with an increased risk of ovarian cancer over multiple years of use.

Dementia
The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported an increased risk of developing probable dementia in post-menopausal women 65 years of age or older during 5.2 years of treatment with daily Conjugated estrogen 0.625 mg alone and during 4 years of treatment with daily Conjugated estrogen 0.625 mg combined with MPA 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger post-menopausal women. (see section **4.2 Posology and Method of Administration-Use in the Elderly** and section, **5.1 Pharmacodynamic Properties-Clinical Efficacy**).

In the absence of comparable data, these risks should be assumed to be similar for other doses of Conjugated estrogen and MPA and other combinations and dosage forms of estrogens and progestins. Because of these risks, 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.

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

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, medication should be withdrawn.

PRECAUTIONS

Fluid retention
Because estrogens may cause some degree of fluid retention, patients with conditions, which might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

Hypertriglyceridemia
In the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, the mean percent increases from baseline in serum triglycerides after one year of treatment with Conjugated estrogen 0.625 mg, 0.45 mg, and 0.3 mg compared with placebo were 34.3, 30.2, 25.1, and 10.7, respectively.

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.

History of cholestatic jaundice
For patients 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.

Elevated blood pressure
In a small number of case reports, substantial increases in blood pressure during ERT have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial a generalized effect of ERT on blood pressure was not seen.

Exacerbation of other conditions
Estrogen replacement therapy may cause an exacerbation of asthma, epilepsy, migraine, diabetes mellitus with or without vascular involvement porphyria, systemic lupus erythematosus and hepatic hemangiomas, and should be used with caution in women with these conditions.

Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use. Addition of a progestin should be considered in women who have undergone hysterectomy but are known to have residual endometriosis, since malignant transformation after estrogen-only therapy has been reported.

Hypocalcemia
Estrogens should be used with caution in individuals with disease that can predispose to severe hypocalcemia.

Hypothyroidism
Patients dependent on thyroid hormone replacement therapy may require increased doses in order to maintain their free thyroid hormone levels in an acceptable range (see section, **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction-*Laboratory Test Interactions***).

Laboratory monitoring
Estrogen administration should be guided by clinical response rather than by hormone levels (e.g., estradiol, FSH).

Latex condoms
Conjugated estrogen has been shown to weaken latex condoms. The potential for Conjugated estrogen to weaken and contribute to the failure of condoms, diaphragms, or cervical caps made of latex or rubber should be considered.

4.5 Drug Interactions

Data from a drug-drug interaction study involving conjugated estrogens and medroxyprogesterone acetate indicate that the pharmacokinetic disposition of both drugs is not altered when the drugs are co-administered. Other clinical drug-drug interaction studies have not been conducted with Conjugated estrogen.

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 preparations (*Hypericum perforatum*), 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-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 17 ß-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.

Interference with laboratory and other diagnostic tests

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

Laboratory test interactions

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

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 anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Estrogens increase thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels by column or by radioimmunoassay or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered.

Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG) leading to increased circulating corticosteroid and sex steroids respectively. Free or biologically active hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentrations, increased triglyceride levels.

Impaired glucose tolerance.

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.

4.6 Use in Special Populations

Pregnancy

Premarin® Vaginal Cream is contraindicated during pregnancy.
If pregnancy occurs during medication with PREMARIN treatment should be withdrawn immediately.

Lactation

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. Caution should be exercised when estrogens are administered to a nursing woman.

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Undesirable Effects

Systemic absorption may occur with the use of Conjugated estrogen vaginal cream. Adverse reactions associated with oral CE treatment should be taken into account.

In a 12-week, randomized, double-blind, placebo-controlled trial of Conjugated estrogen vaginal cream 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 statically significant differences between PVC and placebo.

The following adverse reactions have either been reported with Conjugated estrogen vaginal cream or are undesirable effects associated with estrogens. It is not possible to calculate frequencies for these events based on prescription data for patient exposure because the dose of Conjugated estrogen vaginal cream varies from patient to patient and the product is available worldwide in various sized units.

System Organ Class Adverse Reaction

Reproductive system and breast disorders

Breakthrough bleeding/spotting, dysmenorrhea/pelvic pain, breast pain, tenderness, enlargement, discharge, application site reactions of vulvovaginal discomfort including burning, irritation, and genital pruritus; vaginal discharge; leukorrhea; increased size of uterine leiomyomata, endometrial hyperplasia

Gastrointestinal disorders

Nausea; vomiting; bloating; abdominal pain, pancreatitis; ischemic colitis

Nervous system disorders

Dizziness; headache; migraine; nervousness, cerebrovascular accident/stroke; exacerbation of chorea, neuritis

Musculoskeletal, connective tissue and bone disorders

Arthralgias; leg cramps

Psychiatric disorders

Changes in libido; mood disturbances; irritability; depression, dementia

Vascular disorders

Pulmonary embolism; venous thrombosis

General disorders and administration site conditions

Edema

Skin and subcutaneous tissue disorders

Alopecia, chloasma/melasma; hirsutism; pruritus; rash, erythema multiforme; erythema nodosum

Hepato-biliary disorder

Gallbladder disease, cholestatic jaundice, asymptomatic impaired liver function

Infections and Infestations

Vaginitis, including vaginal candidiasis, cystitis-like syndrome

Neoplasms benign and malignant (including cysts and polyps)

Breast cancer, ovarian cancer, fibrocystic breast changes, endometrial cancer, enlargement of hepatic hemangiomas, growth potentiation of benign meningioma

Immune system disorders

Urticaria, angioedema, hypersensitivity, anaphylactic/anaphylactoid reactions

Metabolism and nutrition disorders

Glucose intolerance, hypocalcemia (in patients with pre-existing conditions of hypocalcemia)

Eye disorders

Intolerance to contact lenses, retinal vascular thrombosis

Cardiac disorders

Myocardial infarction

Investigations

Changes in weight (increase or decrease), increased triglycerides, increases in blood pressure

4.9 Overdose

Symptoms of overdosage of estrogen-containing products in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur in females. There is no specific antidote and further treatment if necessary should be symptomatic.

Contact your physician or local Poison Control Center in case of accidental use of high doses of Premarin Vaginal Cream.

5 PHARMACOLOGICAL PROPERTIES

5.1 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. 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.

Clinical Pharmacology

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. 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 mcg 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 estrogen in post-menopausal women.

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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.

5.2 Pharmacodynamic Properties

Conjugated estrogen vaginal cream contains a mixture of conjugated equine estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, as sodium sulfate conjugates, 17 α-dihydroequilin, 17 α-estradiol, and 17 β-dihydroequilin.

Clinical Efficacy

Effects on vasomotor symptoms
In the first year of the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, a total of 2,805 post-menopausal women (average age 53.3 ± 4.9 years) were randomly assigned to one of eight treatment groups, receiving either placebo or Conjugated estrogen, with or without medroxyprogesterone acetate. Efficacy for vasomotor symptoms was assessed during the first 12 weeks of treatment in a subset of symptomatic women (n = 241) who had at least seven moderate-to-severe hot flushes daily, or at least 50 moderate-to-severe hot flushes during the week before randomization. With Conjugated estrogen (0.3 mg, 0.45 mg, and 0.625 mg tablets), the relief of both the frequency and severity of moderate-to-severe vasomotor symptoms was shown to be statistically improved compared

with placebo at Weeks 4 and 12. Table 1 shows the adjusted mean number of hot flushes in the Conjugated estrogen 0.3 mg, 0.45 mg, and 0.625 mg and placebo treatment groups over the initial 12-week period.

TABLE 1. Summary tabulation of the number of hot flushes per day– mean values and comparisons between the active treatment groups and the placebo group: patients with at least 7 moderate to severe flushes per day or at least 50 per week at baseline, last observation carried forward (LOCF)

Treatment (No. of Patients)	**No. of Hot Flushes/Day**			
Time period (Week)	**Baseline Mean ± SD**	**Observed Mean ± SD**	**Mean Change ± SD**	**p-Values vs. Placebo[a]**
0.625 mg Conjugated estrogen (n = 27)				
4	12.29 ± 3.89	1.95 ± 2.77	-10.34 ± 4.73	<0.001
12	12.29 ± 3.89	0.75 ± 1.82	-11.54 ± 4.62	<0.001
0.45 mg Conjugated estrogen (n = 32)				
4	12.25 ± 5.04	5.04 ± 5.31	-7.21 ± 4.75	<0.001
12	12.25 ± 5.04	2.32 ± 3.32	-9.93 ± 4.64	<0.001
0.3 mg Conjugated estrogen (n = 30)				
4	13.77 ± 4.78	4.65 ± 3.71	-9.12 ± 4.71	<0.001
12	13.77 ± 4.78	2.52 ± 3.23	-11.25 ± 4.60	<0.001
Placebo (n = 28)				
4	11.69 ± 3.87	7.89 ± 5.28	-3.80 ± 4.71	-
12	11.69 ± 3.87	5.71 ± 5.22	-5.98 ± 4.60	-

[a]: Based on analysis of covariance with treatment as factor and baseline as covariate.

Effects on vulvar and vaginal atrophy

Results of vaginal maturation indexes at cycles 6 and 13 showed that the differences from placebo were statistically significant ($p < 0.001$) for all treatment groups.

Effects on atrophic vaginitis

A 12-week, prospective, randomized, double-blind placebo-controlled study was conducted to compare the safety and efficacy of 2 Conjugated estrogen vaginal cream regimens 0.5 g [0.3 mg Conjugated estrogen] administered twice weekly and 0.5 g (0.3 mg Conjugated estrogen) administered sequentially for 21 days on drug followed by 7 days off drug to matching placebo regimens in the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. The initial 12-week, double-blind, placebo-controlled phase was followed by an open-label phase to assess endometrial safety through week 52. The study randomized 423 generally healthy post-menopausal women between 44 to 77 years of age (mean 57.8 years), who at baseline had ≤5 percent superficial cells on a vaginal smear, a vaginal pH ≥5.0, and who identified one most bothersome moderate to severe symptom of vulvar and vaginal atrophy. The majority (92.2 percent) of the women were Caucasian (n = 390); 7.8 percent were Other (n = 33). All subjects were assessed for improvement in the mean change from baseline to Week 12 for the co-primary efficacy

variables of: most bothersome symptom of vulvar and vaginal atrophy (defined as the moderate to severe symptom that had been identified by the woman as most bothersome to her at baseline); percentage of vaginal superficial cells and percentage of vaginal parabasal cells; and vaginal pH.

In the 12-week, double-blind phase, a statistically significant mean change between baseline and Week 12 in the symptom of dyspareunia was observed for both of the Conjugated estrogen vaginal cream regimens (0.5 g daily for 21 days, then 7 days off and 0.5 g twice weekly) compared to matching placebo. Also demonstrated for each Conjugated estrogen vaginal cream regimen compared to placebo was a statistically significant increase in the percentage of superficial cells at Week 12 (28%, 21/7 regimen and 26%, twice weekly, compared to 3% and 1% for matching placebo), a statistically significant decrease in parabasal cells (-61% and -58%, twice weekly, compared to -21% and -7% for matching placebo) and statistically significant mean reduction between baseline and Week 12 in vaginal pH (-1.62, 21/7 regimen and -1.57, twice weekly , compared to -0.36 and -0.26 for matching placebo). In this study there were no statistically significant differences between PVC and placebo.

Endometrial safety was assessed by endometrial biopsy for all randomly assigned subjects at Week 52. For the 155 subjects (83 on the 21/7 regimen, 72 on the twice-weekly regimen) completing the 52-week period with complete follow-up and evaluable endometrial biopsies, there were no reports of endometrial hyperplasia or endometrial carcinoma.

Table 2: Mean Change in Dyspareunia Severity Compared to Placebo MITT Population of Most Bothersome Symptom Score For Dyspareunia, LOCF

Dyspareunia*	PVC 0.5 g 2x/wk[a]	Placebo 0.5 g 2x/wk[a]	PVC 0.5 g 21/7[b]	Placebo 0.5 g 21/7[b]
	n Mean (SD)	n Mean (SD)	n Mean (SD)	n Mean (SD)
Baseline	52 2.43 (0.76)	22 2.28 (1.04)	50 2.26 (0.99)	18 2.32 (0.88)
Week 12	52 0.88 (0.96)	21 1.63 (1.16)	50 0.77 (1.05)	18 1.92 (1.03)
Week 12 Change from Baseline	52 -1.55 (0.92)	21 -0.62 (1.23)	50 -1.48 (1.17)	18 -0.40(1.01)
P-value vs. Placebo	<0.001[c]	--	<0.001[d]	--

[a.] PVC 2x/wk = apply PVC twice a week
[b.] PVC 21/7 = apply PVC for 21 days and then 7 days of no therapy
[c.] Comparison of PVC 2x/wk with placebo 2x/wk
[d.] Comparison of PVC 21/7 with placebo 21/7
* Symptom Assessment Scale: 0 (none), 1 (mild), 2 (moderate), 3 (severe)

Effects on bone mineral density

Health and Osteoporosis, Progestin and Estrogen (HOPE) Study

The HOPE study was a double-blind, randomized, placebo/active-drug-controlled, multicenter study of healthy post-menopausal women with an intact uterus. Subjects (mean age 53.3 ± 4.9 years) were 2.3 ± 0.9 years on average since menopause and took one 600 mg tablet of elemental calcium (Caltrate™) daily. Subjects were not given Vitamin D supplements. They were treated with Conjugated estrogen 0.625 mg, 0.45 mg, 0.3 mg, or placebo. Prevention of bone loss was assessed by measurement of bone mineral density (BMD), primarily at the anteroposterior lumbar spine (L_2 to L_4). Secondarily, BMD measurements of the total body, femoral neck, and trochanter were also analyzed. Serum osteocalcin, urinary calcium, and N-telopeptide were used as bone turnover markers (BTM) at cycles 6, 13, 19, and 26.

Intent-to-treat Subjects

All active treatment groups showed significant differences from placebo in each of the four BMD endpoints at cycles 6, 13, 19, and 26. The percent changes from baseline to final evaluation are shown in Table 3.

TABLE 3. Percent change in bone mineral density: comparison between active and placebo groups in the intent-to-treat population, LOCF

Region evaluated treatment group[a]	No. Of subjects	Baseline (g/cm^2) Mean ± sd	Change from baseline (%) Adjusted mean ± se	P-values Vs. Placebo
L_2 to L_4 BMD				
0.625	83	1.17 ± 0.15	2.46 ± 0.37	<0.001
0.45	91	1.13 ± 0.15	2.26 ± 0.35	<0.001
0.3	87	1.14 ± 0.15	1.13 ± 0.36	<0.001
Placebo	85	1.14 ± 0.14	-2.45 ± 0.36	
Total Body BMD				
0.625	84	1.15 ± 0.08	0.68 ± 0.17	<0.001
0.45	91	1.14 ± 0.08	0.74 ± 0.16	<0.001
0.3	87	1.14 ± 0.07	0.40 ± 0.17	<0.001
Placebo	85	1.13 ± 0.08	-1.50 ± 0.17	
Femoral Neck BMD				
0.625	84	0.91 ± 0.14	1.82 ± 0.45	<0.001
0.45	91	0.89 ± 0.13	1.84 ± 0.44	<0.001
0.3	87	0.86 ± 0.11	0.62 ± 0.45	<0.001
Placebo	85	0.88 ± 0.14	-1.72 ± 0.45	
Femoral Trochanter BMD				
0.625	84	0.78 ± 0.13	3.82 ± 0.58	<0.001
0.45	91	0.76 ± 0.12	3.16 ± 0.56	0.003
0.3	87	0.75 ± 0.10	3.05 ± 0.57	0.005
Placebo	85	0.75 ± 0.12	0.81 ± 0.58	

[a]: Identified by dosage (mg) of Conjugated estrogen or placebo.

Figure 1 shows the cumulative percentage of subjects with changes from baseline equal to or greater than the value shown on the x-axis.

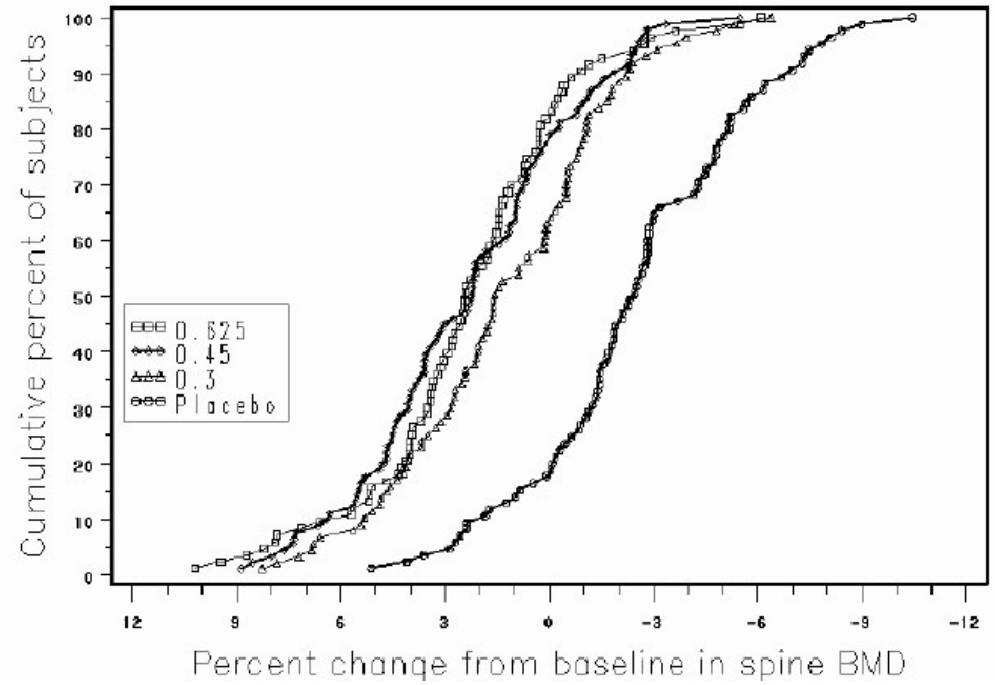

Figure 1. Cumulative percent of subjects with changes from baseline in spine BMD of given magnitude or greater in Conjugated estrogen and placebo groups

The mean percent changes from baseline in L_2 to L_4 BMD for women who completed the bone density study are shown with standard error bars by treatment group in Figure 2. Significant differences between each of the Conjugated estrogen dosage groups and placebo were found at cycles 6, 13, 19, and 26.

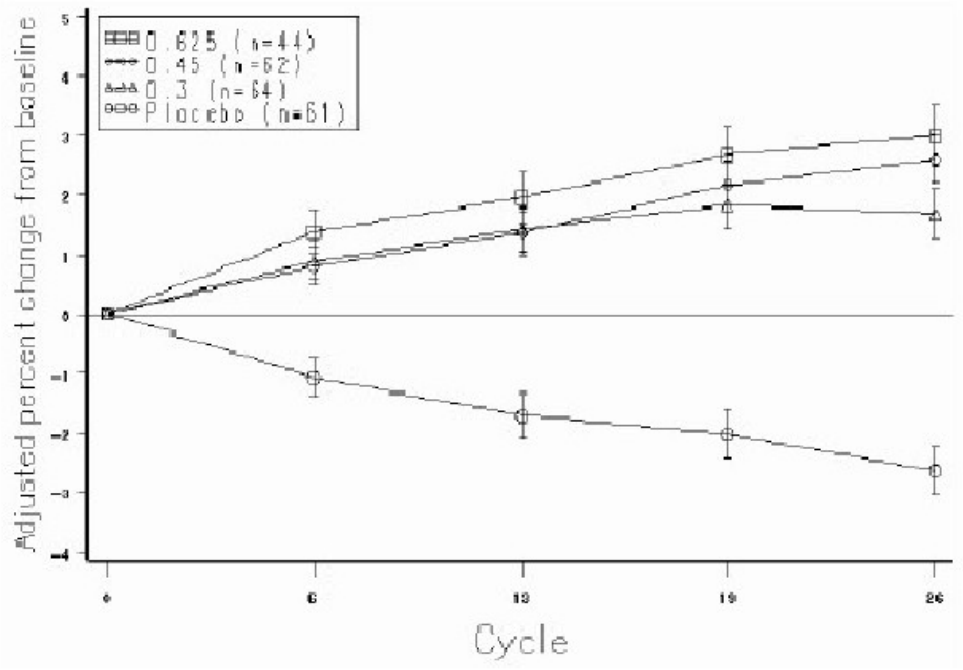

Figure 2. Adjusted mean (SE) percent change from baseline at each cycle in spine BMD: subjects completing in Conjugated estrogen groups and placebo

The bone turnover markers serum osteocalcin and urinary N-telopeptide significantly decreased ($p < 0.001$) in all active-treatment groups at cycles 6, 13, 19, and 26 compared with the placebo group. Larger mean decreases from baseline were seen with the active groups than with the placebo group. Significant differences from placebo were seen less frequently in urine calcium.

Effects on Female Hypogonadism

In clinical studies of delayed puberty due to female hypogonadism, breast development was induced by doses as low as 0.15 mg. The dosage may be gradually titrated upward at 6 to 12-month intervals as needed to achieve appropriate bone age advancement and eventual epiphyseal closure. Available data suggest that chronic dosing with 0.625 mg is sufficient to induce artificial cyclic menses with sequential progestin treatment and to maintain bone mineral density after skeletal maturity is achieved.

Women's Health Initiative Studies (WHI)

The Women's Health Initiative (WHI) enrolled approximately 27,000 predominantly healthy post-menopausal women in two substudies to assess the risks and benefits of Conjugated estrogen [0.625 mg daily] alone or in combination with medroxyprogesterone acetate (MPA) [0.625 mg/2.5 mg daily] compared to placebo. The primary endpoint was the incidence of coronary heart disease (CHD), i.e., non-fatal myocardial infarction (MI), silent MI and coronary death. The primary safety endpoint was incidence of invasive breast

cancer. The substudy did not evaluate the effects of hormone replacement therapy on menopausal symptoms.

The estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen alone in predetermined primary endpoints.

No overall effect on coronary heart disease (CHD) events (defined as non-fatal MI, silent MI, or death, due to CHD) was reported in women receiving estrogen alone compared with placebo. Results of the estrogen-alone substudy, which included 10,739 women (average age of 63 years, range 50 to 79; 75.3% White, 15.1% Black, 6.1% Hispanic, 3.6% Other), after an average follow-up of 6.8 years, are presented in the table below.

In the estrogen-alone substudy of WHI, there was no significant overall effect on the relative risk (RR) of CHD (RR 0.95, 95% nominal confidence interval [nCI] 0.79-1.16); a slightly elevated RR of CHD was reported in the early follow-up period and diminished over time. There was no significant effect on the RR of invasive breast cancer (RR 0.80, 95% nCI 0.62-1.04) or colorectal cancer (RR 1.08, 95% nCI 0.75-1.55) reported. Estrogen use was associated with a statistically significant increased risk of stroke (RR 1.37, 95% nCI 1.09-1.73) and deep vein thrombosis (DVT) (RR 1.47, 95% nCI 1.06-2.06). The RR of PE (RR 1.37, 95% nCI 0.90-2.07) was not significantly increased. A statistically significant reduced risk of hip, vertebral and total fractures was reported with estrogen use (RR 0.65, 95% nCI 0.45-0.94), (RR 0.64, 95% nCI 0.44-0.93), and (0.71, 95% nCI 0.64-0.80), respectively. The estrogen-alone substudy did not report a statistically significant effect on death due to other causes (RR 1.08, 95% nCI 0.88-1.32) or an effect on overall mortality risk (RR 1.04, 95% nCI 0.88-1.22). These confidence intervals are unadjusted for multiple looks and multiple comparisons.

TABLE 4. Relative and absolute risk seen in the estrogen-alone substudy of WHI

Event	**Relative Risk Conjugated estrogen vs. Placebo (95% nci[a])**	**Conjugated estrogen N = 5,310**	**Conjugated estrogen N = 5,429**
		Absolute Risk per 10,000 Person-years	
CHD events [b]	0.95 (0.78-1.16)	57	54
Non-fatal MI [b]	0.91 (0.73-1.14)	43	40
CHD death [b]	1.01 (0.71-1.43)	16	16
All Stroke [c]	1.33 (1.05-1.68)	33	45
Ischemic [b]	1.55 (1.19-2.01)	25	38
Deep vein thrombosis [b,d]	1.47 (1.06-2.06)	15	23
Pulmonary embolism [b]	1.37 (0.90-2.07)	10	14
Invasive breast cancer [b]	0.80 (0.62-1.04)	34	28
Colorectal cancer [c]	1.08 (0.75-1.55)	16	17
Hip fracture [c]	0.65 (0.45-0.94)	19	12

TABLE 4. Relative and absolute risk seen in the estrogen-alone substudy of WHI			
Event	**Relative Risk Conjugated estrogen vs. Placebo (95% nci[a])**	**Conjugated estrogen N = 5,310**	**Conjugated estrogen N = 5,429**
		Absolute Risk per 10,000 Person-years	
Vertebral fractures [c,d]	0.64 (0.44-0.93)	18	11
Lower arm/wrist fractures	0.58 (0.47-0.72)	59	35
Total fractures [c,d]	0.71 (0.64-0.80)	197	144
Death due to other causes[c,e]	1.08 (0.88-1.32)	50	53
Overall mortality [c,d]	1.04 (0.88-1.22)	75	79
Global Index [c,f]	1.02 (0.92-1.13)	201	206

[a] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[b] Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
[c] Not included in global index.
[d] Results are based on an average follow-up of 6.8 years.
[e] All deaths, except from breast or colorectal cancer, definite/probable CHD, PE, or cerebrovascular disease.
[f] A subset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

Table 5 describes the primary results of the Estrogen-alone substudy stratified by age at baseline.

TABLE 5. Women's Health Initiative Estrogen-alone Substudy Results Stratified by Age at Baseline						
AGE						
Endpoint	**50-59 years**		**60-69 years**		**70-79 years**	
	Conjugated estrogen (N = 1637)	**Placebo (N = 1673)**	**Conjugated estrogen (N = 2387)**	**Placebo (N = 2465)**	**Conjugated estrogen (N = 1286)**	**Placebo (N = 1291)**
CHD[a,b]						
Number of cases	21	34	96	106	84	77
Absolute risk (N) [c]	17	27	58	62	98	88
Hazard ratio (95% CI)	0.63 (0.36-1.09)		0.94 (0.71-1.24)		1.13 (0.82-1.54)	
Stroke[b]						
Number of cases	18	21	84	54	66	52
Absolute risk (N) [c]	15	17	51	31	76	59
Hazard ratio(95% CI)	0.89 (0.47-1.69)		1.62 (1.15-2.27)		1.21 (0.84-1.75)	

TABLE 5. Women's Health Initiative Estrogen-alone Substudy Results Stratified by Age at Baseline						
AGE						
Endpoint	**50-59 years**		**60-69 years**		**70-79 years**	
	Conjugated estrogen (N = 1637)	**Placebo (N = 1673)**	**Conjugated estrogen (N = 2387)**	**Placebo (N = 2465)**	**Conjugated estrogen (N = 1286)**	**Placebo (N = 1291)**
DVT[b]						
Number of cases	16	10	39	29	30	20
Absolute risk (N) [c]	13	8	23	17	34	22
Hazard ratio [d] (95% CI)	1.64 (0.74-3.60)		3.02 (1.51-6.06)		4.54 (2.22-9.31)	
VTE [b]						
Number of cases	20	15	54	43	37	28
Absolute risk (N) [c]	16	12	32	25	42	31
Hazard ratio [d] (95% CI)	1.37 (0.70-2.68)		2.82 (1.59-5.01)		3.77 (2.07-6.89)	
Pulmonary Embolism [b]						
Number of cases	12	8	28	17	12	14
Absolute risk (N) [c]	10	6	17	10	14	16
Hazard ratio [d] (95% CI)	1.54 (0.63-3.77)		2.80 (1.28-6.16)		2.36 (0.96-5.80)	
Invasive Breast Cancer						
Number of cases	25	35	42	60	27	29
Absolute risk (N) [c]	21	29	26	36	32	34
Hazard ratio(95% CI)	0.72 (0.43-1.21)		0.72 (0.49-1.07)		0.94 (0.56-1.60)	
Colorectal Cancer						
Number of cases	8	14	26	31	27	13
Absolute risk (N) [c]	7	12	16	19	32	15
Hazard ratio(95% CI)	0.59 (0.25-1.41)		0.88 (0.52-1.48)		2.09 (1.08-4.04)	
Hip Fracture[b]						

TABLE 5. Women's Health Initiative Estrogen-alone Substudy Results Stratified by Age at Baseline						
AGE						
Endpoint	**50-59 years**		**60-69 years**		**70-79 years**	
	Conjugated estrogen (N = 1637)	**Placebo (N = 1673)**	**Conjugated estrogen (N = 2387)**	**Placebo (N = 2465)**	**Conjugated estrogen (N = 1286)**	**Placebo (N = 1291)**
Number of cases	5	1	9	20	32	52
Absolute risk (N) [c]	4	1	5	12	37	58
Hazard ratio(95% CI)	5.02 (0.59-43.02)		0.47 (0.22-1.04)		0.64 (0.41-0.99)	
Total Fractures[b]						
Number of cases	153	173	220	348	167	240
Absolute risk (N) [c]	126	139	132	201	191	269
Hazard ratio (95% CI)	0.90 (0.72-1.12)		0.63 (0.53-0.75)		0.70 (0.57-0.85)	
Overall Mortality[b]						
Number of cases	34	48	129	131	134	113
Absolute risk (N)	28	38	77	75	153	127
Hazard ratio (95% CI)	0.71 (0.46-1.11)		1.02 (0.80-1.30)		1.20 (0.93-1.55)	

[a] CHD defined as myocardial infarction or coronary death.
[b] Based on adjudicated data over a mean duration of therapy of 7.1 years.
[c] Absolute risk is per 10,000 person-years.
[d] VTE hazard ratios compared with women aged 50-59 taking placebo.

Timing of initiation of estrogen therapy from the start of menopause may affect the overall risk-benefit profile. The WHI estrogen-alone substudy stratified by age showed a non-significant trend of reduced risk for CHD and Total Mortality compared with placebo in women who initiated hormone therapy closer to menopause than those initiating therapy more distant from menopause.

Women's Health Initiative Memory Study

In the estrogen-alone Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 2,947 predominantly healthy hysterectomized post-menopausal women aged 65 to 79 years was randomized to Conjugated estrogen (0.625 mg daily) or placebo. The relative risk of probable dementia for Conjugated estrogen alone vs. placebo was 1.49 (95% CI 0.83-2.66). The absolute risk of probable dementia for Conjugated estrogen alone vs. placebo was 37 vs. 25 cases per 10,000 women-years.

Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed types (having features of both AD and VaD). The most common classification of probable dementia in both the treatment and placebo groups was AD. Since the substudy was conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger post-menopausal women (see section, **4.4 Special Warnings and Special Precautions for Use-Dementia** and section, **4.2 Posology and Method of Administration-Use in the Elderly**).

5.3 Pharmacokinetic Properties

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.

Metabolism
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.

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

6 NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology
Acute toxicity studies have been conducted with conjugated estrogens (Premarin®).

Acute Toxicity
Premarin®

In studies conducted by Wyeth, Premarin (125 mg/kg) was administered orally. The LD_{50} value for Premarin® administered orally or intraperitoneally to male and female CD-1 mice and CD rats was greater than 125 mg/kg.

7 DESCRIPTION

PREMARIN® Vaginal Cream contains a mixture of conjugated estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant

mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, sodium sulfate conjugates, 17 α-dihydroequilin, 17 α-estradiol, and 17 β-dihydroequilin.

PREMARIN® Vaginal Cream is applied intravaginally.

8 PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

24 months

8.3 Packaging Information

Conjugated estrogen vaginal cream is available in tubes of 14 g, each gram containing 0.625 mg of conjugated estrogen. Each tube is accompanied with a calibrated plastic applicator.

8.4 Storage and Handling Instructions

Store below 25°C.

Keep out of reach of children. For external (intravaginal) use only.

Instructions for Use and Handling

No Special Instruction

9 PATIENT COUNSELLING INFORMATION

Advise patients that PREMARIN® Vaginal Cream should not be taken if they have any of the conditions mentioned in section **4.3 Contraindications**.

Advise patients that systemic absorption may occur with the use of Conjugated estrogen vaginal cream. Warnings and precautions associated with oral Conjugated estrogen treatment should be taken into account.

Vaginal bleeding: Inform patients of the importance of reporting vaginal bleeding to their healthcare provider as soon as possible.

Possible serious adverse reactions with estrogens: Inform patients of possible serious adverse reactions of estrogen therapy including cardiovascular disorders, malignant neoplasms, and probable dementia.

Possible less serious but common adverse reactions with estrogens: Inform patients of possible less serious but common adverse reactions of estrogen therapy such as headache, breast pain and tenderness, nausea and vomiting.

10 DETAILS OF MANUFACTURER

M/s. PF Consumer Healthcare Canada ULC, 1025 Marcel-Laurin Boulevard, Saint-Laurent, Quebec, Canada, H4R 1J6.

11 DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Import & Marketing Permission No. IMP-962 dated 03 Nov 2003.

12 DATE OF REVISION

January 2023