1. NAME OF THE MEDICINAL PRODUCT

Premarin® Vaginal Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Premarin® (conjugated estrogens) Vaginal Cream – Each gram contains 0.625 mg conjugated estrogens, USP.

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, as sodium sulfate conjugates, 17 α-dihydroequilin, 17 α-estradiol, and 17 β-dihydroequilin.

3. PHARMACEUTICAL FORM

Cream formulation

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

Premarin (conjugated estrogens, CE) Vaginal Cream is indicated in the treatment of atrophic vaginitis, dyspareunia and kraurosis vulvae.

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia (see **Section 4.4 Special Warnings and Precautions** and **Section 4.8 Undesirable Effects**).

4.2 Posology and Method of Administration

Use of Premarin Vaginal Cream, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Post-menopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

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.

A woman without a uterus does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin.

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

Treatment of Dyspareunia
Premarin Vaginal Cream (0.5 g) is administered intravaginally in a twice-weekly (for example, Monday and Thursday) continuous regimen or in a cyclic regimen of 21 days of therapy followed by 7 days off of

therapy.

Use in children
Premarin Vaginal Cream is not indicated in children**.**

Use in elderly patients
There have not been sufficient numbers of geriatric women involved in clinical studies utilizing Premarin Vaginal Cream to determine whether those over 65 years of age differ from younger subjects in their response to Premarin Vaginal Cream.

The Women's Health Initiative Study (WHI)
In the WHI estrogen-alone substudy (daily CE [0.625 mg] versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age (see **Section 5.1 Pharmacodynamic Properties, WHI Studies**).

The Women's Health Initiative Memory Study (WHIMS)
In the WHIMS of post-menopausal women 65 to 79 years of age, there was increased risk of developing probable dementia in women receiving estrogen alone when compared to placebo. It is unknown whether this finding applies to younger postmenopausal women (see **Section 4.4 Special Warnings and Precautions – *Dementia*** and **Section 5.1 Pharmacodynamic Properties, WHIM Study**).

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.

4.3 Contraindication

1. Known or suspected pregnancy (see **Section 4.6. Fertility, Pregnancy and Lactation**).
2. Undiagnosed abnormal uterine bleeding.
3. Known, suspected, or history of breast cancer.
4. Known or suspected estrogen-dependent neoplasia (e.g., endometrial cancer, endometrial hyperplasia).
5. Active or history of confirmed arterial thromboembolic disease (e.g., stroke, myocardial infarction) or venous thromboembolism (such as deep venous thrombosis, pulmonary embolism).
6. Active or chronic liver dysfunction or disease.
7. Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency).
8. Hypersensitivity to any component of this medication.

4.4 Special Warnings and Precautions for Use

General
CE Vaginal Cream: Systemic absorption may occur with the use of CE vaginal cream. Warnings and precautions associated with oral CE treatment should be taken into account (See below and **Section 4.8**

Undesirable Effects).

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.

Cardiovascular risk
Menopausal hormone therapy (MHT) 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.

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

Stroke
In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) compared to women receiving placebo (45 versus. 33 per 10,000 women-years). The increase in risk was demonstrated in year one and persisted.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg) versus those receiving placebo (18 versus 21 per 10,000 women-years).

Should a stroke occur or be suspected, Premarin Vaginal Cream should be discontinued immediately (see **Section 5.1 Pharmacodynamic Properties**).

Venous thromboembolism (VTE)
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 venous thromboembolism (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, Premarin Vaginal Cream should be discontinued immediately (see section 5.1 Pharmacodynamic properties).

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.

If feasible, Premarin Vaginal Cream 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 Precautions for Use - *Exacerbation of other conditions*** and **Section 5.1 Pharmacodynamic Properties**).

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 MHT 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 Precautions for Use - *General***).

Clinical surveillance of all women taking estrogen or estrogen-plus-progestin combinations is important. Adequate diagnostic measures 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 WHI (see **Section 5.1 Pharmacodynamic Properties**). In the estrogen-alone substudy of WHI, after an average of 7.1 years of follow-up, CE (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. A large meta-analysis of observational studies reported that when estrogen-alone therapy or estrogen-plus-progestin therapy was taken for more than 5 years, the increased risk of breast cancer may persist for 10 years or more after discontinuation of treatment. The reported risk at 10 years or more after discontinuation of treatment was not increased when therapy was taken for less than 5 years. In current users the increased risk of breast cancer in women taking estrogen-alone or combined estrogen-progestin for MHT becomes apparent after about 1-4 years. The risk did not vary by the type of estrogen in estrogen-alone preparations.

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

Ovarian cancer
In some epidemiologic studies, the use of estrogen-therapy has been associated with an increased risk of ovarian cancer over multiple years of use. Other epidemiologic studies have not found these associations.

Dementia
The estrogen-alone arm of the WHIMS, an ancillary study of WHI that enrolled post-menopausal women between the ages of 65 - 79 years reported a relative risk (HR) of probable dementia for conjugated estrogens alone versus placebo of 1.49 [HR 1.49 (95% CI 0.83-2.66)] (see **Section 5.1 Pharmacodynamic Properties**).

It is unknown whether these findings apply to younger post-menopausal women.

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

Hypercalcemia
Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

Immune

Angioedema

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

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 CE 0.625 mg, 0.45 mg, 0.3 mg and placebo were 34.2, 30.2, 25.0, and 10.8, 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.

Impaired liver function and 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. Estrogens may be poorly metabolized in patients with impaired liver function.

Elevated blood pressure

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

Exacerbation of other conditions

Estrogen therapy may cause an exacerbation of asthma, epilepsy, migraine with or without aura, otosclerosis, porphyria, systemic lupus erythematosus, and hepatic hemangiomas, and should be used with caution in women with these conditions.

Endometriosis may be exacerbated with administration of estrogen therapy. 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.

Hypocalcemia

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

Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients dependent on thyroid hormone therapy, who are receiving estrogens, may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range (see **Section 4.5 Interaction with other Medicinal Products and other Forms of Interaction**).

Laboratory monitoring

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

FSH).

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

4.5 Interaction with other Medicinal Products and Other Forms of Interaction
Data from a drug-drug interaction study involving conjugated estrogens and medroxyprogesterone acetate (MPA) 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 estrogens.

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.

Lamotrigine:
Hormonal contraceptives containing estrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. The same interaction has been reported in women taking lamotrigine along with MHT containing estrogens.

Interference with Laboratory and Other Diagnostic Tests

Laboratory Test Interactions
Increased platelet count; decreased levels of antithrombin III, and 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.

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.

4.6 Fertility, Pregnancy and Lactation

Pregnancy
Premarin Vaginal Cream should not be used during pregnancy (see **Section 4.3 Contraindication**).

If pregnancy occurs during medication with Premarin Vaginal Cream treatment should be withdrawn immediately.

Lactation
Premarin Vaginal Cream should not be used during 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

Adverse reactions are listed in the Table in CIOMS frequency categories:

Very Common:	≥10%
Common:	≥1% and <10%
Uncommon:	≥0.1% and <1%
Rare:	≥0.01% and <0.1%
Very rare:	<0.01%
Unknown	Cannot be estimated from the available data

Systemic absorption may occur with the use of CE 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 CE 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 CE vaginal cream-21/7 treatment group (0.5 g CE vaginal cream daily for 21 days, then 7 days off), 72 women in the matching placebo treatment group; 140 women in the CE vaginal cream-2x/wk treatment group (0.5 g CE vaginal cream 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 CE vaginal cream, including those subjects randomized at baseline to placebo. In this study there were no statistically significant differences between CE vaginal cream and placebo.

The following adverse reactions have either been reported with CE 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 CE vaginal cream varies from patient to patient and the product is available worldwide in various sized units.

TABLE 1: CE VAGINAL CREAM ADVERSE DRUG REACTION TABLE

System Organ Class	Adverse Drug Reactions
Infections and infestations	Vaginitis, including vaginal candidiasis; cystitis-like syndrome

TABLE 1: CE VAGINAL CREAM ADVERSE DRUG REACTION TABLE

System Organ Class	Adverse Drug Reactions
Neoplasms benign, malignant and unspecified (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
Endocrine disorders	Precocious puberty
Metabolism and nutrition disorders	Glucose intolerance; hypocalcemia (in patients with preexisting conditions of hypocalcemia)
Psychiatric disorders	Changes in libido; mood disturbances; irritability; depression; dementia
Nervous system disorders	Dizziness; headache; migraine; nervousness; cerebrovascular accident/stroke; exacerbation of chorea
Eye disorders	Intolerance to contact lenses; retinal vascular thrombosis
Cardiac disorders	Myocardial infarction
Vascular disorders	Pulmonary embolism; venous thrombosis
Gastrointestinal disorders	Nausea; vomiting; bloating; abdominal pain; pancreatitis; ischemic colitis
Hepatobiliary disorders	Gallbladder disease; cholestatic jaundice
Skin and subcutaneous tissue disorders	Alopecia; chloasma/melasma; hirsutism; pruritus; rash; erythema multiforme; erythema nodosum
Musculoskeletal and connective tissue disorders	Arthralgia; leg cramps
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; leucorrhea; gynecomastia in males; increased size of uterine leiomyomata; endometrial hyperplasia
General disorders and administration site conditions	Edema
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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of Action

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, which is secreted by the adrenal cortex, to estrone in the peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens 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 postmenopausal women.

Pharmacodynamics

Currently, there are no pharmacodynamic data known for CE alone.

Effects on vasomotor symptoms

In the first year of the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, a total of 2,805 postmenopausal women (average age 53.3 ± 4.9 years) were randomly assigned to one of eight treatment groups, receiving either placebo or conjugated estrogens, 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 CE (0.3 mg, 0.45 mg, and 0.625 mg tablets), the decrease 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 2 shows the observed mean number of hot flushes in the CE 0.3 mg, 0.45 mg, and 0.625 mg and placebo treatment groups over the initial 12-week period.

TABLE 2. SUMMARY TABULATION OF THE NUMBER OF HOT FLUSHES PER DAY – MEAN VALUES AND COMPARISONS BETWEEN THE CE 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, EFFICACY EVALUABLE (EE) POPULATION

Treatment (No. of Patients)	**---------- No. of Hot Flushes/Day ----------**			
Time Period (week)	**Baseline Mean ± SD**	**Observed Mean ± SD**	**Mean Change ± SE[a]**	**p-Values vs. Placebo[a]**
0.625 mg CE				
4 (n=27)	12.29 ± 3.89	1.95 ± 2.77	-10.34 ± 0.90	<0.001
12 (n=26)	12.03 ± 3.73	0.45 ± 0.95	-11.58 ± 0.88	<0.001
0.45 mg CE				
4 (n=32)	12.25 ± 5.04	5.04 ± 5.31	-7.21 ± 0.83	<0.001
12 (n=30)	12.49 ± 5.11	2.33 ± 3.39	-10.16 ± 0.82	<0.001
0.3 mg CE				

TABLE 2. SUMMARY TABULATION OF THE NUMBER OF HOT FLUSHES PER DAY – MEAN VALUES AND COMPARISONS BETWEEN THE CE 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, EFFICACY EVALUABLE (EE) POPULATION

Treatment (No. of Patients)	---------- No. of Hot Flushes/Day ----------			
Time Period (week)	Baseline Mean ± SD	Observed Mean ± SD	Mean Change ± SE[a]	p-Values vs. Placebo[a]
4 (n=30)	13.77 ± 4.78	4.65 ± 3.71	-9.12 ± 0.85	<0.001
12 (n=29)	13.83 ± 4.86	2.20 ± 2.73	-11.63 ± 0.83	<0.001
Placebo				
4 (n=28)	11.69 ± 3.87	7.89 ± 5.28	-3.80 ± 0.88	-
12 (n=25)	11.61 ± 3.79	5.27 ± 4.97	-6.34 ± 0.89	-

[a.] Standard errors based on assumption of equal variances.

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.

CE Vaginal Cream: Effect on atrophic vaginitis.

A 12-week, prospective, randomized, double blind placebo-controlled study was conducted to compare the safety and efficacy of 2 conjugated estrogens vaginal cream regimens 0.5 g [0.3 mg CE] administered twice weekly and 0.5 g (0.3 mg CE) 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 postmenopausal women between 44 to 77 years of age (mean 57.8 years), who at baseline had ≤5% 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%) of the women were Caucasian (n = 390); 7.8% 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 estrogens vaginal cream regimens (0.5 g daily for 21 days, then 7 days off and 0.5 g twice weekly) compared to matching placebo; see Table 3. Also demonstrated for each conjugated estrogens 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 respectively, compared to 3% and 1% for matching placebo), a statistically significant decrease in parabasal cells (-61% , 21/7 regimen and -58%, twice weekly respectively, compared to -22% 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, respectively, compared to -0.36 and -0.26 for matching placebo). In this study there were no statistically significant differences between CE vaginal

cream and placebo.

Endometrial safety was assessed by endometrial biopsy for all randomly assigned subjects at week 52. For the 155 subjects (82 on the 21/7 regimen, 73 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 3: MEAN CHANGE IN DYSPAREUNIA SEVERITY COMPARED TO PLACEBO MITT POPULATION OF MOST BOTHERSOME SYMPTOM SCORE FOR DYSPAREUNIA, LOCF

Dyspareunia*	**CE Vaginal Cream 0.5 g 2x/wk[a]**	**Placebo 0.5 g 2x/wk[a]**	**CE Vaginal Cream 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)**
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. CE Vaginal Cream 2x/wk = apply CE Vaginal Cream twice a week.
b. CE Vaginal Cream 21/7 = apply CE Vaginal Cream for 21 days and then 7 days of no therapy.
c. Comparison of CE Vaginal Cream 2x/wk with placebo 2x/wk.
d. Comparison of CE Vaginal Cream 21/7 with placebo 21/7.
* Symptom Assessment Scale: 0 (none), 1 (mild), 2 (moderate), 3 (severe).

Effect 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 postmenopausal 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 CE 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 (L2 to L4). 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 4.

TABLE 4. PERCENT CHANGE IN BONE MINERAL DENSITY: COMPARISON BETWEEN CE 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-Value vs. Placebo**
L_2 to L_4 BMD				
0.625	83	1.17 ± 0.15	2.32 ± 0.35	<0.001
0.45	91	1.13 ± 0.15	2.08 ± 0.34	<0.001
0.3	87	1.14 ± 0.15	1.24 ± 0.34	<0.001

TABLE 4. PERCENT CHANGE IN BONE MINERAL DENSITY: COMPARISON BETWEEN CE 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-Value vs. Placebo**
Placebo	85	1.14 ± 0.14	-2.46 ± 0.35	
Total body BMD				
0.625	84	1.15 ± 0.08	0.66 ± 0.17	<0.001
0.45	91	1.14 ± 0.08	0.71 ± 0.16	<0.001
0.3	87	1.14 ± 0.07	0.37 ± 0.16	<0.001
Placebo	85	1.13 ± 0.08	-1.52 ± 0.16	
Femoral neck BMD				
0.625	84	0.91 ± 0.14	1.74 ± 0.43	<0.001
0.45	91	0.89 ± 0.13	1.95 ± 0.41	<0.001
0.3	87	0.86 ± 0.11	0.57 ± 0.42	<0.001
Placebo	85	0.88 ± 0.14	-1.81 ± 0.43	
Femoral trochanter BMD				
0.625	84	0.78 ± 0.13	3.78 ± 0.57	<0.001
0.45	91	0.76 ± 0.12	3.46 ± 0.54	<0.001
0.3	87	0.75 ± 0.10	3.19 ± 0.55	0.003
Placebo	85	0.75 ± 0.12	0.93 ± 0.56	

[a.] Identified by dosage (mg) of CE or placebo.
BMD = Bone mineral density; L_2 to L_4 = anteroposterior lumbar spine; LOCF = Last observation carried forward; SD = Standard deviation; SE = Standard error.

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.

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 CE [0.625 mg daily] alone or in combination with MPA [0.625 mg/2.5 mg daily] compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease [(CHD) defined as non-fatal myocardial infarction (MI), silent MI and CHD death], with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other causes. The study did not evaluate the effects of CE alone or CE plus MPA on menopausal symptoms.

WHI Estrogen-alone Substudy
The WHI 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.

Results of the estrogen-alone substudy, which included 10,739 women (average age of 63.6 years, range 50 to 79; 75.3% White, 15.1% Black, 6.1% Hispanic, 3.6% Other), after an average follow-up of 7.1 years, are presented in Table 5 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] 0.78-1.16); 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 1.33, 95% nCI 1.05-1.68) 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 (RR 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 5. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN-ALONE SUBSTUDY OF WHI

Event	Relative Risk CE vs. Placebo (95% nCI[b])	Placebo n = 5,429	CE n = 5,310
		Absolute Risk per 10,000 Women-Years	
CHD events[c]	0.95 (0.78–1.16)	57	54
Non-fatal MI[c]	*0.91 (0.73–1.14)*	*43*	*40*
CHD death[c]	*1.01 (0.71–1.43)*	*16*	*16*
All Strokes[b]	1.33 (1.05–1.68)	33	45
Ischemic stroke[c]	*1.55 (1.19–2.01)*	*25*	*38*
Deep vein thrombosis[c,d]	1.47 (1.06–2.06)	15	23
Pulmonary embolism[c]	1.37 (0.90–2.07)	10	14
Invasive breast cancer[c]	0.80 (0.62–1.04)	34	28
Colorectal cancer[e]	1.08 (0.75–1.55)	16	17
Hip fracture[c]	0.65 (0.45–0.94)	19	12
Vertebral fractures[c,d]	0.64 (0.44–0.93)	18	11
Lower arm/wrist fractures[c,d]	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[e,f]	1.08 (0.88–1.32)	50	53
Overall mortality[c,d]	1.04 (0.88–1.22)	75	79
Global Index[g]	1.02 (0.92–1.13)	201	206

[a] Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.

[b] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

[c] Results are based on centrally adjudicated data for an average follow-up of 7.1 years.

[d] Not included in global index.

[e] Results are based on an average follow-up of 6.8 years.

[f] All deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease.

[g] 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.

Primary results of the Estrogen-alone substudy stratified by age at baseline is described in the following Table 6.

TABLE 6. WOMEN'S HEALTH INITIATIVE ESTROGEN-ALONE SUBSTUDY RESULTS STRATIFIED BY AGE AT BASELINE AGE

Endpoint	50-59 years		60-69 years		70-79 years	
	CE (N=1637)	Placebo (N=1673)	CE (N=2387)	Placebo (N=2465)	CE (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)	
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	25	35	42	60	27	29

TABLE 6. WOMEN'S HEALTH INITIATIVE ESTROGEN-ALONE SUBSTUDY RESULTS STRATIFIED BY AGE AT BASELINE AGE						
Endpoint	**50-59 years**		**60-69 years**		**70-79 years**	
	CE (N=1637)	**Placebo (N=1673)**	**CE (N=2387)**	**Placebo (N=2465)**	**CE (N=1286)**	**Placebo (N=1291)**
cases						
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]						
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	73	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)[c]	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 or 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 the initiation of MHT relative to the start of menopause may affect the overall risk-benefit profile. The WHI estrogen-alone substudy stratified by age showed in women 50-59 years of age, a non-significant trend towards reduced risk for CHD and overall mortality compared with placebo in women who initiated MHT closer to menopause than those initiating therapy more distant from menopause.

Observational Studies of Breast Cancer Risk

A large meta-analysis of observational studies generated evidence for the type and timing of MHT on breast cancer risk. After ceasing MHT, some excess risk persisted for more than 10 years; its magnitude depended on the duration of previous use.

It was reported that, when estrogen-alone therapy or estrogen-plus-progestin therapy was taken for more than 5 years, the increased risk may persist for 10 years or more after discontinuation of treatment:

MHT type	**Time passed since discontinuation of MHT**	**Duration of MHT therapy**	**Risk ratio (95% CI)**
Estrogen-alone	≥10 years	5-9 years	1.14 (1.04-1.25)
	≥10 years	≥10 years	1.29 (1.16-1.42)
Estrogen+progestin	≥10 years	5-9 years	1.19 (1.10-1.28)
	≥10 years	≥10 years	1.28 (1.15-1.43)

The reported risk at 10 years or more after discontinuation of treatment was not increased when therapy was taken for less than 5 years:

MHT type	**Time passed since discontinuation of MHT**	**Duration of MHT therapy**	**Risk ratio (95% CI)**
Estrogen-alone	≥10 years	<1 year	0.99 (0.87-1.12)
	≥10 years	1-4 years	1.04 (0.95-1.13)
Estrogen+progestin	≥10 years	<1 year	1.06 (0.95-1.19)
	≥10 years	1-4 years	1.09 (1.00-1.18)

In current users, the increased risk of breast cancer in women taking estrogen-alone or combined estrogen-progestin MHT becomes apparent after about 1-4 years:

MHT type	**Duration of MHT therapy**	**Risk ratio (95% CI)**
Estrogen-alone	<1 year	1.08 (0.86-1.35)
	1-4 years	1.17 (1.10-1.26)
Estrogen+progestin	<1 year	1.20 (1.01-1.43)
	1-4 years	1.60 (1.52-1.69)

The risk did not vary by the type of estrogen in estrogen-alone preparations:

Estrogen-alone MHT by constituent	**Duration of MHT therapy**	**Risk ratio (95% CI)**
Equine estrogen	5-14 years	1.32 (1.25-1.39)
Estradiol	5-14 years	1.38 (1.30-1.46)

Women's Health Initiative Memory Study

The estrogen-alone Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, enrolled 2,947 predominantly healthy hysterectomized post-menopausal women 65 years of age and older (45% were 65 to 69 years of age; 36% were 70 to 74 years of age; and 19% were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) in the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus. placebo was 1.49 (95 percent CI 0.83-2.66). The absolute risk of probable dementia for CE alone versus. 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 65 to 79 years of age, it is unknown whether these findings apply to younger post-menopausal women (see **Section 4.4 Special Warnings and Precautions for Use** - ***Dementia*** and **Section 5.1 Pharmacodynamic Properties, WHIM Study**).

5.2 Pharmacokinetic Properties

Absorption

Conjugated estrogens are water soluble and are well-absorbed through the skin, mucous membranes, and the gastrointestinal (GI) tract. The vaginal delivery of estrogens circumvents first-pass metabolism.

A bioavailability study was conducted in 24 postmenopausal women with atrophic vaginitis. The mean (SD) pharmacokinetic parameters for unconjugated estrone, unconjugated estradiol, total estrone, total estradiol and total equilin following 7 once-daily doses of Premarin Vaginal Cream 0.5 g is shown in the Table 7 below.

TABLE 7. MEAN ± SD PHARMACOKINETIC PARAMETERS OF PREMARIN FOLLOWING DAILY ADMINISTRATION (7 DAYS) OF PREMARIN VAGINAL CREAM 0.5 G IN 24 POSTMENOPAUSAL WOMEN

Pharmacokinetic Profiles of Unconjugated Estrogens Premarin Vaginal Cream 0.5 g			
PK Parameters Arithmetic Mean ± SD	**C_{max} (pg/mL)**	**T_{max} (hr)**	**AUC_{ss} (pg•hr/mL)**
Estrone	42.0 ± 13.9	7.4 ± 6.2	826 ± 295
Baseline-adjusted estrone	21.9 ± 13.1	7.4 ± 6.2	365 ± 255
Estradiol	12.8 ± 16.6	8.5 ± 6.2	231 ± 285
Baseline-adjusted estradiol	9.14 ± 14.7	8.5 ± 6.2	161 ± 252
Pharmacokinetic Profiles of Conjugated Estrogens Premarin Vaginal Cream 0.5 g			
PK Parameters Arithmetic Mean ± SD	**C_{max} (ng/mL)**	**T_{max} (hr)**	**AUC_{ss} (ng•hr/mL)**
Total estrone	0.60 ± 0.32	6.0 ± 4.0	9.75 ± 4.99
Baseline-adjusted total estrone	0.40 ± 0.28	6.0 ± 4.0	5.79 ± 3.7
Total estradiol	0.04 ± 0.04	7.7 ± 5.9	0.70 ± 0.42
Baseline-adjusted total estradiol	0.04 ± 0.04	7.7 ± 6.0	0.49 ± 0.38
Total equilin	0.12 ± 0.15	6.1 ± 4.7	3.09 ± 1.37

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 SHBG and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is a major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine

followed by reabsorption. In post-menopausal women a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

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

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

5.3 Preclinical Safety Data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Active Ingredient: Estrogens, conjugated.

Inactive Ingredients: Glycerin, Water Purified, Mineral Oil, Cetyl Alcohol, Propylene Glycol Monostearate, Glyceryl Monostearate Self Emulsifying, White Wax, Phenylethyl Alcohol, Cetyl Esters Wax, Methyl Stearate, Nitrogen, Sodium Lauryl Sulphate.

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

Refer to product outer carton for expiry date.

6.4 Special Precautions for Storage

Store at below 25°C.

Keep out of reach of children.

Store in place that is not exposed to light.

Dispense in light resistant containers.

6.5 Nature and Contents of Container

Combination package: Each contains Net Wt. 14 g tube with one plastic applicator calibrated in ½g increments to a maximum of 2 g.

6.6 Special Precautions for Disposal and Other Handling

Not applicable

7. MANUFACTURER

PF Consumer Healthcare Canada ULC
1025 Boulevard Marcel Laurin
St-Laurent QC H4R 1J6
Canada

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