1. NAME OF THE MEDICINAL PRODUCT
Premarin® vaginal cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Conjugated Estrogens

3. PHARMACEUTICAL FORM
Vaginal Cream

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Premarin Vaginal Cream is indicated in the treatment of atrophic vaginitis, dyspareunia and kraurosis vulvae.

ET (estrogen therapy) and HT (hormone therapy) should not be initiated or continued to prevent coronary heart disease (see section **4.4 Special warnings and precautions for use, Cardiovascular risk**).

The benefits and risks of estrogen therapy must always be carefully weighed, including consideration of the emergence of risks as therapy continues (see see section **4.4 Special warnings and precautions for use**). In particular when considering use of estrogen therapy in women without menopausal symptoms, or for long-term use, alternative treatments should be considered.

For many years it has been known that topical or vaginal estrogen therapy would stimulate cell growth and development, improving the epithelial thickness of the vaginal mucosa and increasing secretions. Recent reports have shown that the intravaginal use of topical estrogen creams produces even higher blood estrogen levels than comparable oral doses. Therefore, precautions recommended with oral estrogen administration should also be observed with this route.

4.2 Posology and method of administration
Administered cyclically for short-term use only: For the treatment of atrophic vaginitis, dyspareunia or kraurosis vulvae.

In patients with severe cases of atrophic vaginitis, the mucosa should first be conditioned with a short course of oral therapy – 1.25 mg daily for approximately 10 days. Vaginal treatment should be instituted at the lowest effective dosage, and the requirement for estrogen therapy reassessed regularly. In patients already receiving oral therapy, the oral dosage may be reduced taking into account the potential absorption from the vaginal medication. The degree of atrophy is directly responsible for the level of absorption and should be the guiding factor in dose adjustment.

Usual dosage range: 0.5 to 2 g daily, intravaginally or topically, depending on the severity of the condition. Administration should be cyclic (e.g., three weeks on and one week off).

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

Patients should be re-evaluated periodically to determine if treatment for symptoms is still necessary.

Pediatric Use
CE 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 to determine whether those over 65 years of age differ from younger subjects in their response to Premarin.

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

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

4.4 Special warnings and precautions for use
General
Estrogen Therapy (ET) has been reported to increase the risk of stroke and deep venous thrombosis (DVT).

ET should not be initiated or continued to prevent coronary heart disease.

The benefits and risks of ET must always be carefully weighed, including consideration of the emergence of risks as therapy continues. 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. In the absence of comparable data, the risks of ET should be assumed to be similar for all estrogens and estrogen/progestin combinations.

Before Premarin is administered, the patient should have a complete physical examination including blood pressure determination. Breasts and pelvic organs should be examined and a Papanicolaou smear taken.

The first follow-up examination should be done preferably within six months after initiation of treatment. Thereafter, examinations should be made once a year and should include those procedures outlined above.

If any surgical procedures are performed, the pathologist should be advised of the patient's therapy when specimens are sent for examination. Liver function tests should be made periodically in subjects who have, or are suspected of having, hepatic disease.

Systemic absorption may occur with the use of Conjugated Estrogens (CE) vaginal cream. Warnings, precautions and adverse reactions associated with oral CE treatment should be taken into account (See below and section **4.8 Undesirable effects**).

Cardiovascular risk
ET 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 Women's Health Initiative (WHI) estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily conjugated estrogen (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 should be discontinued immediately (see section **5.1 Pharmacodynamic properties**).

Coronary heart disease
In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as non-fatal myocardial infarction [MI], silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo.

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years). An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5.

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 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 should be discontinued immediately (see section **5.1 Pharmacodynamic properties**).

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was observed during the first year and persisted.

If visual abnormalities develop, discontinue Premarin 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 should be permanently discontinued. Retinal vascular thrombosis has been reported in patients receiving estrogens with or without progestins.

If feasible, Premarin 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.

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 ET 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**.**

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**). 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, and appeared to return to baseline within approximately five years after stopping treatment (only the observational studies have substantial data on risk after stopping).

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

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for estrogen plus progestin compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years for estrogen plus progestin compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for estrogen plus progestin compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations.

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 Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, that enrolled post-menopausal women between the ages of 65-79, 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 estrogen therapy has been reported.

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

Physical examination
Before initiating or reinstating ET, a complete personal and family medical history should be taken, together with a thorough general and gynecological examination guided by the contraindications and warnings for use. Before starting treatment pregnancy should be excluded. Periodic check-ups and careful benefit/risk evaluations should be undertaken in women treated with ET therapy.

Estrogen administration should be guided by clinical response rather than by hormone levels (eg, estradiol, FSH).

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, and 0.3 mg compared with placebo were 34.2, 30.2, 25.0, and 10.8 percent increase from baseline, 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 ET have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial a generalized effect of ET on blood pressure was not seen.

Exacerbation of other conditions
Estrogen therapy may cause an exacerbation of asthma, epilepsy, migraine with or without aura, diabetes mellitus, 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.

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.

Palliative therapy in men
Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of non-fatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

Hypothyroidism
Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients dependent on thyroid hormone replacement 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.

Uterine bleeding
Certain patients may develop abnormal uterine bleeding (see section **4.4 Special warnings and precautions for use, Malignant neoplasms, Endometrial cancer**).

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 estrogens 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, possible resulting in a decreased in therapeutic effects and/or changes in the uterine bleeding profile. CYP3A4 inhibitors such as cimetidine, erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Interference with Laboratory and Other Diagnostic Tests

Laboratory test interactions
Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Premarin should not be used during pregnancy (see section **4.3 Contraindications**).

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

Lactation

Premarin 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

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 conjugated estrogens (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 conjugated estrogens 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 estrogens vaginal cream varies from patient to patient and the product is available worldwide in various sized units.

CE VAGINAL CREAM ADVERSE DRUG REACTION TABLE

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

Description

Premarin (conjugated estrogens CSD) is a mixture of 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. Premarin contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

Premarin Vaginal Cream contains a mixture of conjugated estrogens, which are a mixture of sodium estrone sulfate and sodium equilin sulfate and other components including sodium sulfate conjugates: 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin. Premarin Vaginal Cream also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, water purified, and mineral oil.

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 post-menopausal 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 post-menopausal women.

Pharmacodynamics

Currently, there are no pharmacodynamic data known for Conjugated Estrogens (CE) alone.

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.

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 post-menopausal 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 1. 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 1. 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).

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 conjugated estrogens (CE) alone [0.625 mg per day] or in combination with medroxyprogesterone acetate (MPA) [0.625 mg/2.5 mg per day]) 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 pre-determined 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 2 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% nCI1.05-1.68) 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 2: RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN- ALONE SUBSTUDY OF WHI[a]

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 stroke[c]	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

TABLE 2: RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN- ALONE SUBSTUDY OF WHI[a]			
		Placebo n = 5,429	CE n = 5,310
Event	Relative Risk CE vs. Placebo (95% nCI[b])	Absolute Risk per 10,000 Women-Years	
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.

Table 3 describes the primary results of the Estrogen-alone substudy stratified by age at baseline.

TABLE 3: 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

TABLE 3: 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)**
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]						
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)[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 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 the initiation of estrogen therapy 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 hormone therapy closer to menopause than those initiating therapy more distant from menopause.

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 aged 65 years of age and older (45 percent were 65 to 69 years of age; 36 percent were 70 to 74 years of age; and 19 percent 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% 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 sub-study was conducted in women 65 to79 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. The estrogens are generally eliminated in near-parallel fashion, with half-lives ranging from 10-20 hours, when corrected for endogenous concentrations as needed.

A bioavailability study was conducted in 24 post-menopausal 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 Table 4 below.

TABLE 4: Mean ± SD Pharmacokinetic Parameters of PREMARIN Following Daily Administration (7 Days) of PREMARIN Vaginal Cream 0.5g in 24 Post-menopausal 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 sex hormone-binding globulin (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 portion of the circulating estrogens exists 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.

Specific Populations

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mineral Oil, Propylene Glycol Monostearate, Glyceryl Monostearate, Glycerin, Cetyl Esters Wax, Cetyl Alcohol, White Wax, Methyl Stearate, Phenylethyl Alcohol, Sodium Lauryl Sulfate, Purified Water

6.2 Nature and contents of container

Each tube contains 14 g conjugated estrogens CSD cream with calibrated plastic applicator. Each gram contains conjugated estrogens CSD 0.625 mg.

6.3 Special precautions for storage

Store below 25°C.

Keep out of the reach of children.

7. PRODUCT OWNER

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