PREMARIN

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1. NAME OF THE MEDICINAL PRODUCT
Premarin®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Conjugated Estrogens

3. PHARMACEUTICAL FORM
Tablets

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
1. Moderate to severe vasomotor symptoms associated with estrogen deficiency.
2. Prevention and management of osteoporosis associated with estrogen deficiency. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate. When prescribing solely for the management of postmenopausal osteoporosis, non-estrogen medications should be first considered.
3. Atrophic vaginitis and atrophic urethritis. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
4. Female hypoestrogenism.

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 ET and HT must always be carefully weighed, including consideration of the emergence of risks as therapy continues (see section **4.4 Special warnings and precautions for use**). 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 HT should be assumed to be similar to all estrogens and estrogen/progestin combinations.

4.2 Posology and method of administration
Administration of Premarin may be continuous (e.g., without a break in therapy) or cyclic (e.g., three weeks on and one week off).

The lowest effective dose should be administered. Patients should be re-evaluated periodically to determine if treatment for symptoms is still necessary.

Since progestogens are administered to reduce the risk of hyperplastic changes of the endometrium, patients without a uterus do not require a progestogen for this purpose.

If an estrogen is prescribed for a postmenopausal woman with a uterus, the addition of a progestin may be appropriate (see section **4.4 Special warnings and 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 precautions for use, Exacerbation of other conditions**).

Tablets should be taken whole; do not divide, crush, chew, or dissolve tablets in mouth.

Dosage adjustment may be made based on individual patient response.

Vasomotor symptoms and/or vulvar and vaginal atrophy
- Consider topical vaginal products when treating solely for vulvar and vaginal atrophy.

Female hypoestrogenism
- Administer cyclically (e.g., three weeks on and one week off).

Use in children
Safety and effectiveness in pediatric patients have not been established. Estrogen treatment of prepubertal girls induces premature breast development and vaginal cornification, and may induce uterine bleeding.

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

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 conjugated estrogens [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) of postmenopausal 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 postmenopausal women (see section **4.4 Special warnings and precautions for use, Dementia** and section **5.1 Pharmacodynamic properties, WHIM Study**).

Usual dosage range
VASOMOTOR SYMPTOMS, ATROPHIC VAGINITIS AND ATROPHIC URETHRITIS ASSOCIATED WITH ESTROGEN DEFICIENCY: 0.3-1.25 mg daily.

OSTEOPOROSIS: 0.3-0.625 mg. Dosage adjustment may be made based upon the individual clinical and bone mineral density responses. This dose should be periodically reassessed by the healthcare provider.

FEMALE HYPOESTROGENISM: 0.3-1.25 mg daily. Administer cyclically (e.g., three weeks on and one week off). Doses are adjusted depending on the severity of symptoms and responsiveness of the endometrium. Doses of 0.15 mg have been used in girls and are associated with the onset of development of secondary sex characteristics. Dose should be individualized to achieve optimum patient response.

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

4.4 Special warnings and precautions for use

General

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.

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

ET has been shown 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 estrogen (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 nonfatal 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 medroxyprogesterone acetate (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 (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 should be discontinued immediately (see section **5.1 Pharmacodynamic properties**).

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 withdrawn. Retinal vascular thrombosis has been reported in patients receiving estrogens with or without progestins.

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 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 (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 ET is discontinued. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer (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 postmenopausal 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 after several years of use. The risk increased with duration of use. Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

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
Ovarian cancer is much rarer than breast cancer. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking estrogen-only or combined estrogen-progestogen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

Some other studies, including the WHI trial, suggest that the use of combined HRTs may be associated with a similar or slightly smaller risk.

Dementia
The estrogen-alone arm of the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, that enrolled postmenopausal women between the ages of 65 to 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 postmenopausal 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.

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

Physical examination
Before initiating or reinstating ET/HT, 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/HT therapy.

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 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 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 also 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 (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, follicle stimulating hormone [FSH]).

Pre-existing uterine leiomyomata may increase in size during estrogens use. There is no adequate evidence that estrogens are effective for nervous symptoms or depression, which may occur during menopause, and they should not be used to treat such conditions.

Patients should be advised that the resumption of menses associated with estrogen replacement therapy in postmenopausal women is not indicative of fertility.

Premarin is not a contraceptive. Women of child-bearing potential desiring contraception should be advised to adhere to non-hormonal contraceptive methods.

Mutagenesis and carcinogenesis
Long-term, continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina and liver.

4.5 Interaction with other medicinal products and other forms of interaction
Data from a drug-drug interaction study involving conjugated equine 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*) preparation, 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.

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.

Estrogens 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
The most serious adverse reactions associated with the use of estrogens are indicated under section **4.4 Special warnings and precautions for use**. The following additional adverse reactions have been reported with estrogen therapy.

Adverse reactions are listed in the Table 1 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

TABLE 1. CE TABLET ADVERSE DRUG REACTION TABLE	
System Organ Class	**Adverse Drug Reaction**
Infections and infestations	
Uncommon	Vaginitis, including vaginal candidiasis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare	Breast cancer; ovarian cancer; fibrocystic breast changes; growth potentiation of benign meningioma
Very rare	Endometrial cancer; enlargement of hepatic hemangiomas
Immune system disorders	
Uncommon	Hypersensitivity
Rare	Urticaria; angioedema; anaphylactic/anaphylactoid reactions
Metabolism and nutrition disorders	
Rare	Glucose intolerance
Very rare	Exacerbation of porphyria; hypocalcemia (in patients with disease that can predispose to severe hypocalcemia)
Psychiatric disorders	
Uncommon	Changes in libido; mood disturbances; depression; dementia
Rare	Irritability
Nervous system disorders	
Uncommon	Dizziness; headache; migraine; nervousness
Rare	Cerebrovascular accident/stroke; exacerbation of epilepsy
Very rare	Exacerbation of chorea
Eye disorders	
Uncommon	Intolerance to contact lenses
Very rare	Retinal vascular thrombosis
Cardiac disorders	
Rare	Myocardial infarction

TABLE 1. CE TABLET ADVERSE DRUG REACTION TABLE	
System Organ Class	**Adverse Drug Reaction**
Vascular disorders	
Uncommon	Venous thrombosis; pulmonary embolism
Rare	Superficial thrombophlebitis
Respiratory, thoracic and mediastinal disorders	
Rare	Exacerbation of asthma
Gastrointestinal disorders	
Uncommon	Nausea; bloating; abdominal pain
Rare	Vomiting; pancreatitis; ischemic colitis
Hepatobiliary disorders	
Uncommon	Gallbladder disease
Very rare	Cholestatic jaundice
Skin and subcutaneous tissue disorders	
Common	Alopecia
Uncommon	Chloasma/melasma; hirsutism; pruritus; rash
Very rare	Erythema multiforme; erythema nodosum
Musculoskeletal and connective tissue disorders	
Common	Arthralgia; leg cramps
Reproductive system and breast disorders	
Common	Abnormal uterine bleeding; breast pain, tenderness, enlargement, discharge; leucorrhea
Uncommon	Change in menstrual flow; change in cervical ectropion and secretion
Rare	Dysmenorrhea/pelvic pain; galactorrhea; increased size of uterine leiomyomata
Very rare	Endometrial hyperplasia
Unknown	Gynecomastia in males
General disorders and administration site conditions	
Uncommon	Edema
Investigations	
Common	Changes in weight (increase or decrease); increased triglycerides
Very rare	Increases in blood pressure

Ovarian cancer
Use of estrogen-only or combined estrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section **4.4 Special warnings and precautions for use**).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2,000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2,000 users will be diagnosed with ovarian cancer over a 5-year period.

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 tablets, USP) for oral administration 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, 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin.

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 conjugated estrogen 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 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				
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.

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 3.

TABLE 3. 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

TABLE 3. 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**
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
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.

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 postmenopausal women in two substudies to assess the risks and benefits of conjugated estrogens (CE) [0.625 mg daily] alone or in combination with medroxyprogesterone acetate (MPA) [0.625 mg/2.5 mg daily] compared to placebo in 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 4 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 1.05-1.8) 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 4. 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
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.

TABLE 4. 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	
[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 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**	
	CE (N=1,637)	**Placebo (N=1,673)**	**CE (N=2,387)**	**Placebo (N=2,465)**	**CE (N=1,286)**	**Placebo (N=1,291)**
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 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)	

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**	
	CE (N=1,637)	**Placebo (N=1,673)**	**CE (N=2,387)**	**Placebo (N=2,465)**	**CE (N=1,286)**	**Placebo (N=1,291)**
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 postmenopausal 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 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women (see section **4.4 Special warnings and precautions for use, Dementia**).

5.2 Pharmacokinetic properties

Absorption
Conjugated estrogens are water-soluble and are well-absorbed from the gastrointestinal tract after release from the drug formulation. The Premarin tablet releases conjugated estrogens slowly over several hours. Maximum plasma concentrations are achieved approximately 6-10 hours following CE

tablet administration. The estrogens are generally eliminated in near-parallel fashion, with half-lives ranging from 10-20 hours, when corrected for endogenous concentrations as needed.

Table 6 below summarizes the mean pharmacokinetic parameters for unconjugated and conjugated estrogens following administration of 1 x 0.625 mg and 1 x 1.25 mg tablets to healthy postmenopausal women.

The pharmacokinetics of Premarin 0.45 mg and 1.25 mg tablets were assessed following a single dose with a high-fat breakfast and with fasting administration. The C_{max} and AUC of estrogens were altered approximately 3 to 13 percent. The changes to C_{max} and AUC are not considered clinically meaningful.

TABLE 6. PHARMACOKINETIC PARAMETERS FOR PREMARIN

Pharmacokinetic Profile of Unconjugated Estrogens Following a Dose of 1 x 0.625 mg				
PK Parameter Arithmetic Mean (%CV)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)
Estrone	87 (33)	9.6 (33)	50.7 (35)	5557 (59)
Baseline-adjusted estrone	64 (42)	9.6 (33)	20.2 (40)	1723 (52)
Equilin	31 (38)	7.9 (32)	12.9 (112)	602 (54)
Pharmacokinetic Profile of Conjugated Estrogens Following a Dose of 1 x 0.625 mg				
PK Parameter Arithmetic Mean (%CV)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
Total Estrone	2.7 (43)	6.9 (25)	26.7 (33)	75 (52)
Baseline-adjusted total estrone	2.5 (45)	6.9 (25)	14.8 (35)	46 (48)
Total Equilin	1.8 (56)	5.6 (45)	11.4 (31)	27 (56)
Pharmacokinetic Profile of Unconjugated Estrogens Following a Dose of 1 x 1.25 mg				
PK Parameter Arithmetic Mean (%CV)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)
Estrone	124 (30)	10.0 (32)	38.1 (37)	6332 (44)
Baseline-adjusted estrone	102 (35)	10.0 (32)	19.7 (48)	3159 (53)
Equilin	59 (43)	8.8 (36)	10.9 (47)	1182 (42)
Pharmacokinetic Profile of Conjugated Estrogens Following a Dose of 1 x 1.25 mg				
PK Parameter Arithmetic Mean (%CV)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
Total Estrone	4.5 (39)	8.2 (58)	26.5 (40)	109 (46)
Baseline-adjusted total estrone	4.3 (41)	8.2 (58)	17.5 (41)	87 (44)
Total equilin	2.9 (42)	6.8 (49)	12.5 (34)	48 (51)

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 postmenopausal 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
0.3 mg Tablets: Opadry, Green, 15B21511 (HPMC 2910, Quinoline Yellow Aluminum Lake, Macrogol, FD&C Blue #2 Indigo Carmine Aluminum Lake, Titanium Dioxide, Polysorbate 80); Hypromellose; Lactose Monohydrate; Magnesium Stearate; Microcrystalline Cellulose; Hydroxypropyl Cellulose; Polyethylene Glycol 400; Sucrose; Opacode WB NS-78-18011 (Purified Water, Titanium Dioxide, Propylene Glycol, Isopropyl Alcohol, HPMC 2910), White Ink; Carnauba Wax; Purified Water.

0.625 mg Tablets: Opadry, Maroon, 03B16083 (HPMC 2910, FD&C Red #40/Allura Red AC Aluminium Lake, Titanium Dioxide, Macrogol, FD&C Blue #2 Indigo Carmine Aluminum Lake); Hypromellose; Lactose Monohydrate; Magnesium Stearate; Microcrystalline Cellulose; Hydroxypropyl Cellulose; Polyethylene Glycol 400; Sucrose; Opacode WB NS-78-18011 (Purified Water, Titanium Dioxide, Propylene Glycol, Isopropyl Alcohol, HPMC 2910), White Ink; Carnauba Wax; Purified Water.

6.2 Nature and contents of container
0.3 mg green tablets are supplied in blisters of 28.

0.625 mg maroon tablets are supplied in blister packs of 28.

Not all presentations may be available locally.

6.3 Special precautions for storage
Do not store above 30°C.

Keep out of reach of children.

7. PRODUCT OWNER
Pfizer Inc
235 East 42nd Street
New York 10017
USA

PRE-SIN-0922/0
Date of last revision: September 2022

Package leaflet: Information for the patient

Premarin Tablet 0.625 mg
conjugated estrogens

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Premarin Tablet is and what it is used for

Premarin Tablet is a Hormone Therapy (HT). It contains the female hormone estrogen. Premarin Tablet is used for:

- Relief of symptoms occurring after menopause. During the menopause, the amount of the estrogen produced by a woman's body drops. This can cause symptoms such as hot face, neck and chest ("hot flushes"). Premarin Tablet alleviates these symptoms after menopause. You will only be prescribed Premarin Tablet if your symptoms seriously hinder your daily life.

- Prevention and management of osteoporosis (thin weak bones) associated with estrogen deficiency. If you use Premarin Tablet only to prevent or treat osteoporosis due to menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you.

- Treatment of inflammation of vagina or urethra associated with estrogen deficiency. If you use Premarin Tablet only to treat changes in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.

- Treatment of estrogen deficiency in female.

2. What you need to know before you take Premarin Tablet

Medical history and regular check-ups

The use of HT carries risks which need to be considered when deciding whether to start taking it, or whether to carry on taking it.

Before you start (or restart) HT, your doctor will ask about your own and your family's medical history. Your doctor may decide to perform a physical examination. This may include an examination of your breasts and/or an internal examination, if necessary.

Once you have started on Premarin Tablet, you should see your doctor for regular check-ups (at least once a year). At these check-ups, discuss with your doctor the benefits and risks of continuing with Premarin Tablet.

Go for regular breast screening, as recommended by your doctor e.g., yearly breast examinations by healthcare provider and monthly breast self-examinations.

Do not take Premarin Tablet

Do not start taking Premarin Tablet if any of the following applies to you. If you are not sure about any of the points below, **talk to your doctor** before taking Premarin Tablet.

- If you have or have ever had breast cancer, or if you are suspected of having it.
- If you have cancerous or non-cancerous tumor which is sensitive to estrogens, such as cancer of the lining of the womb (endometrial cancer) or excessive thickening of the womb lining (endometrial hyperplasia), or if you are suspected of having it.
- If you are pregnant or think you may be pregnant.
- If you have any unexplained vaginal bleeding.
- If you have or have had a disease caused by blood clots in the arteries, such as a stroke or heart attack.
- If you have or have had a blood clot in a vein (thrombosis), such as in the legs (deep venous thrombosis) or the lungs (pulmonary embolism).
- If you are allergic (hypersensitive) to conjugated estrogens or any of the other ingredients of this medicine, of you are suspected of having it.
- If you have liver dysfunction or disease.
- If you have a blood clotting disorder (such as protein C, protein S, or antithrombin deficiency).

If any of the above conditions appear for the first time while taking Premarin Tablet, stop taking it at once and consult your doctor immediately.

Warnings and precautions

Talk to your doctor before taking Premarin Tablet if you have or ever had any of the following problems, before you start the treatment, as these may return or become worse during treatment with Premarin Tablet. If so, you should see your doctor more often for check-ups.

- Increased risk of developing blood clots such as blood clot in a deep vein, usually in the leg (deep venous thrombosis); clot in a blood vessel in the lungs which can cause chest pain, breathlessness and fainting (pulmonary embolism); or stroke.
- Heart attack (myocardial infarction).

- Growth of womb lining outside your womb (endometriosis), excessive thickening of the womb lining (endometrial hyperplasia), or cancer of the womb lining (endometrial cancer).
- Gallbladder disease.
- Fluid retention due to cardiac or kidney problems.
- A very high level of fat in your blood (hypertriglyceridemia).
- High blood pressure.
- Asthma.
- Epilepsy.
- Migraine or severe headaches.
- Diabetes.
- A disease affecting the eardrum and hearing (otosclerosis).
- An inability to break down chemicals called porphyrins (porphyria).
- A disease of the immune system that affects many organs of the body (systemic lupus erythematosus, SLE).
- A liver disorder (e.g., a benign liver tumor).
- Low blood calcium levels (hypocalcaemia).
- High blood calcium levels (hypercalcemia).
- An underactive thyroid gland with tiredness, weight gain, and skin and hair changes (hypothyroidism).
- Fibroids inside your womb.

Stop taking Premarin Tablet and see a doctor immediately

If you notice any of the following when taking HT:

- Any of the conditions mentioned in the "Do not take Premarin Tablet" section.
- If you become pregnant.
- If you notice signs of a blood clot, such as:
  - Painful swelling and redness of the legs.
  - Sudden chest pain.
  - Difficulty in breathing.

  For more information, see section "Blood clots in a vein (thrombosis)" below.
- Migraine with unusual visual or other sensory experiences.

- Visual abnormalities such as sudden partial or complete loss of vision, or a sudden onset of bulging eyes (proptosis), double vision (diplopia).

- Persistent or recurring abnormal vaginal bleeding.

- Rapid swelling under the skin, in areas such as the face, throat, arms and legs, which can be life threatening if throat swelling blocks the airway. This condition is called angioedema.

- Yellowing of the skin or the whites of your eyes (jaundice). These may be signs of a liver disease.

- A large rise in your blood pressure (symptoms may be headache, tiredness, dizziness).

Effects of HT on your heart or circulation

Blood clots in a vein (thrombosis)

HT has been shown to increase the risk of deep venous thrombosis (DVT).

Blood clots can be serious and if one travels to the lungs, it can cause chest pain, breathlessness, collapse or even death. This condition is called pulmonary embolism, or PE.

DVT and PE are examples of a condition called venous thromboembolism, or VTE.

For signs of a blood clot, see section "Stop taking Premarin Tablet and see a doctor immediately" above.

If you're going to have surgery, make sure your doctor knows about it or tell the surgeon that you are taking Premarin Tablet. You may need to stop taking Premarin Tablet at least 4 to 6 weeks before the operation, or during periods of prolonged immobilization, to reduce the risk of a blood clot. Your doctor will tell you when you can start taking Premarin Tablet again.

Heart disease (heart attack)

HT is not recommended for women who have heart disease, or have had heart disease recently. If you have ever had heart disease, talk to your doctor to see if you should be taking HT.

There is no evidence that HT will prevent a heart attack.

If you get a pain in your chest that spreads to your arm or neck, **see a doctor as soon as possible and do not take any more HT** until your doctor says you can. This pain could be a sign of heart disease.

Stroke

Estrogen therapy (ET) has been shown to increase the risk of stroke.

If you are worried, or **if you have had a stroke in the past,** talk to your doctor to see if you should take HT.

If you get unexplained migraine-type headaches, with unusual visual or other sensory experiences, **see a doctor as soon as possible and do not take any more HT** until your doctor says you can. These headaches may be an early warning sign of a stroke.

HT and cancer

Excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer)

Taking estrogen-only HT will increase the risk of excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the womb lining (endometrial cancer).

Adding a progestin to postmenopausal ET has been shown to reduce the risk of excessive thickening of the lining of the womb (endometrial hyperplasia), which may be a precursor to cancer of the womb lining (endometrial cancer).

Breast cancer

Women who have breast cancer, or have had breast cancer in the past, should not take HT.

Evidence shows that taking estrogen-progestin or estrogen-only HT increases the risk of breast cancer. The extra risk depends on how long you take use HT. After stopping HT, the extra risk will decrease with time, but the risk may persist for 10 years or more if you have used HT for more than 5 years.

Regularly check your breasts. See your doctor if you notice any changes such as:

- Dimpling of the skin.
- Changes in the nipple.
- Any lumps you can see or feel.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer. The use of estrogen-only or combined estrogen-progestogen HT has been associated with a slightly increased risk of ovarian cancer.

Other conditions

There is some evidence of a higher risk of memory loss in postmenopausal women aged 65 to 79 (dementia).

Women with hypertriglyceridemia may experience large increases of their plasma triglycerides, which can lead to inflammation of the pancreas (pancreatitis). Symptoms of pancreatitis may include abdominal pain, abdominal swelling, fever and feeling or being sick.

If you are taking thyroid hormone replacement therapy (e.g., thyroxine), your doctor may monitor your thyroid function more often when you start treatment.

The resumption of menses associated with estrogen replacement therapy in postmenopausal women is not indicative of fertility.

Premarin Tablet is not a contraceptive. Women of child-bearing potential desiring contraception should adhere to non-hormonal contraceptive methods.

HT may affect some medical tests. If you visit a hospital or clinic for any medical tests, you should tell the doctor concerned that you are taking HT.

Other medicines and Premarin Tablet

Some medicines may interfere with the effect of Premarin Tablet. This might lead to irregular bleeding. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription, herbal remedies or other natural products. The medicines listed in this leaflet may not be the only ones that could interact with Premarin Tablet.

Tell your doctor if you are taking:

- A herbal preparation such as St. John's wort (*Hypericum perforatum*).
- An anticonvulsant used to treat epilepsy (phenobarbital, phenytoin, carbamazepine).
- An anti-infective used to treat tuberculosis (rifampicin) or HIV (ritonavir).
- A corticosteroid (dexamethasone).
- Cimetidine (used to treat stomach ulcers and reduce stomach acid).
- An antibiotic used to treat bacterial infections (erythromycin, clarithromycin).
- Anti-fungal medicines (ketoconazole, itraconazole).
- Metyrapone (most commonly used in the treatment of Cushing's syndrome).

The way that Premarin Tablet works may be altered if these medicines are used at the same time.

Premarin Tablet with food and drink

Drinking grapefruit juice may affect the way that your medicine works.

Laboratory tests

If you need a blood test, tell your doctor or the laboratory staff that you are taking Premarin Tablet, because this medicine can affect the results of some tests.

Pregnancy, breast-feeding and fertility

Premarin Tablet should not be used during pregnancy and lactation.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

There is no evidence to suggest that taking Premarin Tablet will affect your ability to drive or to operate machinery.

Premarin Tablet contains lactose monohydrate and sucrose

Lactose monohydrate and sucrose are sugars. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Premarin Tablet

Starting to take Premarin Tablet

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Administration of Premarin Tablet may be continuous (e.g., without a break in therapy) or cyclic (e.g., three weeks on and one week off).

Your doctor will aim to give you the lowest dose for the shortest time to treat your symptoms for as short as necessary. Speak to your doctor if you think this dose is too strong or not strong enough.

Your doctor will re-evaluate you periodically to determine if treatment for symptoms is still necessary.

Premarin Tablet should be taken whole; do not divide, crush, chew, or dissolve tablets in mouth.

Dosage adjustment may be made based on your response.

Take your tablet at the same time each day as this will help to remind you to take your medicine.

The recommended dose

Vasomotor symptoms, inflammation of vaginal/urethra associated with estrogen deficiency

0.3-1.25 mg daily. Your doctor will prescribe the lowest dose (0.3 mg) that will control your symptoms. If your symptoms are not adequately controlled, higher doses can be used.

Osteoporosis

For the treatment of osteoporosis, your doctor may advise you to use 0.3-0.625 mg each day. Your doctor should review the need for treatment regularly.

Estrogen deficiency in female

0.3-1.25 mg daily. Administer cyclically (e.g., three weeks on and one week off). Your doctor may adjust the dose depending on the severity of symptoms and responsiveness of the endometrium (womb lining).

Pediatric population

Safety and effectiveness in pediatric patients have not been established.

While you are taking Premarin Tablet

If you have not had a hysterectomy (surgical removal of uterus), you doctor may prescribe progestin in addition to Premarin Tablet. In some cases, hysterectomized women (women without a uterus) with a history of endometriosis (growth of womb lining outside your womb) may need a progestin.

If you take more Premarin Tablet than you should

If you take too many tablets, don't worry. You may feel some nausea (sickness), vomiting, breast tenderness, dizziness, abdominal pain and drowsiness/fatigue. If you have not had a hysterectomy, you may experience a short period of vaginal bleeding, but it is unlikely that serious problems will occur. If you are concerned, talk to your doctor or pharmacist.

If you forget to take Premarin Tablet

If you forget to take a tablet don't worry. Take it as soon as you remember and then carry on taking the remaining tablets at the usual time.

Do not take a double dose to make up for a forgotten tablet.

Missed tablets may cause a short period of light bleeding in women who have not had a hysterectomy.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you experience any of the following symptoms after taking this medicine.

Uncommon (may affect up to 1 in 100 people)
- Allergic reactions which may cause swelling of the face, lips, mouth, tongue and/or throat and difficulty breathing.
- Blood clots in the veins of the legs (painful swelling and redness of the legs).
- Blood clots in the veins of the lungs (sudden chest pain, difficulty breathing).

Rare (may affect up to 1 in 1,000 people)
- Rapid swelling under the skin, in areas such as the face, throat, arms and legs, which can be life threatening if throat swelling blocks the airway.
- Sudden, severe allergic reaction with breathing difficulty, swelling, lightheadedness, fast heartbeat, sweating and loss of consciousness.
- Stroke.
- Worsening of epilepsy.
- Heart attack (chest pain or discomfort, shortness of breath).
- A worsening of asthma.
- Pancreatitis (abdominal pain, abdominal swelling, fever and feeling or being sick).

Very rare (may affect less than 1 in 10,000 people)
- A worsening of an inability to break down chemicals called porphyrins. This causes abdominal pain, chest pain, vomiting, confusion, constipation, fever, high blood pressure, high heart rate, or skin blisters/itching.
- Sudden partial or complete loss of vision or other problems with your eyesight.

Other side effects that may occur are:

Common (may affect up to 1 in 10 people)
- Hair loss.
- Abnormal uterine bleeding.
- Breast pain, breast tenderness, swollen breasts, discharge from the nipples.
- Vaginal discharge.
- Joint pain, leg cramps.
- Changes in weight (increase or decrease).
- Changes in your triglyceride levels (fatty substances in the blood).

Uncommon (may affect up to 1 in 100 people)
- Vaginal inflammation, including vaginal candidiasis.
- Changes in your interest in sex (increased or decreased libido).
- Mood disturbances, depression, nervousness.
- Memory loss.
- Dizziness.
- Headache, migraine.

- Difficulty wearing contact lenses.
- Feeling sick, bloating, abdominal pain.
- Gallbladder disease.
- Excessive hair (in parts where there is usually very little or no hair).
- Rash, itchiness.
- Dark patches on the skin.
- Change in menstrual flow.
- Change in cervical ectropion and secretion (cells lining inside of the cervical canal spread on the outside of the cervix and appears red and discharges mucus).
- Fluid retention.

Rare (may affect up to 1 in 1,000 people)
- Breast cancer.
- Ovarian cancer.
- Changes in breast tissue.
- Growth of non-cancerous tumor which forms from the membranes that surround the brain and spinal cord.
- Itchy rash.
- An intolerance to glucose.
- Irritability.
- Inflammation of the vein near the surface of the skin caused by blood clot.
- Vomiting.
- Inflammation of the colon (part of the intestine) which may present as lower left sided abdominal pain and/or bloody diarrhea.
- Period pain.
- Pelvic pain.
- Spontaneous flow of milk from the breast (unassociated with childbirth or nursing).
- Increased size of fibroid inside the womb.

Very rare (may affect less than 1 in 10,000 people)
- Cancer of the lining of the womb (endometrial cancer).
- Enlargement of non-cancerous tumor on the surface of the liver.
- Low blood levels of calcium (hypocalcemia) in patients with disease that can predispose to severe hypocalcemia.
- A worsening of chorea (an existing neurological disorder characterized by involuntary spasmodic movements of the body).
- Jaundice (e.g., yellowing of the skin or the whites of your eyes).
- Red patches on the skin.
- Excessive thickening of the womb lining.
- Increases in blood pressure.

Not known (frequency cannot be estimated from available data)
- Abnormal non-cancerous enlargement of one or both breasts in males.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Premarin Tablet

Keep out of reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP.

Do not store above 30°C.

6. Contents of the pack and other information

What Premarin Tablet contains

- The active substance is a mixture of hormones called conjugated estrogens.
- Premarin Tablet is available in two different strengths:
  - 0.3 mg tablets: Each tablet contains 0.3 mg conjugated estrogens.
  - 0.625 mg tablets: Each tablet contains 0.625 mg conjugated estrogens.

- The other ingredients are:
  - 0.3 mg tablets: Opadry, Green, 15B21511 (HPMC 2910, Quinoline Yellow Aluminum Lake, Macrogol, FD&C Blue #2 Indigo Carmine Aluminum Lake, Titanium Dioxide, Polysorbate 80); Hypromellose; Lactose Monohydrate; Magnesium Stearate; Microcrystalline Cellulose; Hydroxypropyl Cellulose; Polyethylene Glycol 400; Sucrose; Opacode WB NS-78-18011 (Purified Water, Titanium Dioxide, Propylene Glycol, Isopropyl Alcohol, HPMC 2910), White Ink; Carnauba Wax; Purified Water.
  - 0.625 mg tablets: Opadry, Maroon, 03B16083 (HPMC 2910, FD&C Red #40/Allura Red AC Aluminium Lake, Titanium Dioxide, Macrogol, FD&C Blue #2 Indigo Carmine Aluminum Lake); Hypromellose; Lactose Monohydrate; Magnesium Stearate; Microcrystalline Cellulose; Hydroxypropyl Cellulose; Polyethylene Glycol 400; Sucrose; Opacode WB NS-78-18011 (Purified Water, Titanium Dioxide, Propylene Glycol, Isopropyl Alcohol, HPMC 2910), White Ink; Carnauba Wax; Purified Water.

What Premarin Tablet looks like and contents of the pack

Premarin Tablet 0.3 mg is a green tablet marked with “0.3”; supplied in blister packs of 28 tablets.

Premarin Tablet 0.625 mg is a maroon tablet marked with “0.625”; supplied in blister packs of 28 tablets.

Not all presentations may be available locally.

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