PRODUCT MONOGRAPH

# [Pr]pms-CONJUGATED ESTROGENS CSD

(conjugated estrogens tablets, CSD)
0.3 mg, 0.625 mg, 0.9 mg, and 1.25 mg

ESTROGENIC HORMONES

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## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| oral | conjugated estrogen tablets 0.3 mg, 0.625 mg, 0.9 mg and 1.25 mg | *For a complete listing see Dosage Forms, Composition and Packaging section.* |

### INDICATIONS AND CLINICAL USE

pms-Conjugated Estrogens CSD (conjugated estrogens tablets, C.S.D.) is indicated for the following:

1. the relief of menopausal and postmenopausal symptoms occurring in naturally or surgically induced estrogen deficiency states including vulvar and vaginal atrophy.
2. the prevention of osteoporosis in naturally occurring or surgically induced estrogen-deficiency states. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy with pms-Conjugated Estrogens CSD should be considered in light of other available therapies (see Boxed Warning) and should only be considered for women at significant risk of osteoporosis. Non-estrogen medications should be carefully considered. For older women who are not experiencing any more acute symptoms of menopause, use in combination with a progestin should only be considered for women who failed on, or were intolerant of, non-estrogen medication. Adequate diet, calcium and vitamin D intake, cessation of smoking, as well as regular physical weight-bearing exercise are required in addition to the administration of pms-Conjugated Estrogens CSD. Postmenopausal women require an average of 1000 mg to 1500 mg/day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.
3. hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.
4. atrophic vaginitis
5. vulvar atrophy (with or without pruritis). **When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.**

pms-Conjugated Estrogens CSD should be prescribed with an appropriate dosage of a progestin for women with intact uteri, in order to prevent endometrial hyperplasia/carcinoma.

**ERT and HRT should not be initiated or continued to prevent cardiovascular disease or dementia (see WARNINGS: Cardiovascular risk and Dementia).**

**The benefits and risks of ERT and HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues (see WARNINGS). 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 HRT should be assumed to be similar for all estrogens and estrogen/progestin combinations.

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

**Pediatrics (< 16 years of age):** pms-Conjugated Estrogens CSD is not indicated for use in children.

## CONTRAINDICATIONS

pms-Conjugated Estrogens CSD (conjugated estrogens tablets, C.S.D.) should not be administered to patients with any of the following conditions:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Liver dysfunction or disease as long as liver function tests have failed to return to normal.
- Known or suspected estrogen-dependent malignant neoplasia (e.g. endometrial cancer).
- Endometrial hyperplasia.
- Known, suspected, or past history of breast cancer.
- Undiagnosed abnormal genital bleeding.
- Known or suspected pregnancy (see Special Populations Pregnant Women).
- Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis.
- Active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease).
- Partial or complete loss of vision due to ophthalmic vascular disease.

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

The Women's Health Initiative (WHI) trial examined the health benefits and risks of oral combined *estrogen plus progestin* therapy (n=16,608) and oral *estrogen-alone* therapy (n=10,739) in postmenopausal women aged 50 to 79 years.[15, 21, 22]

The *estrogen plus progestin* arm of the WHI trial (mean age 63.3 years) indicated an increased risk of *myocardial infarction* (MI), *stroke, invasive breast cancer, pulmonary emboli* and *deep vein thrombosis* in postmenopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day) for 5.2 years compared to those receiving placebo.[22]

The *estrogen-alone* arm of the WHI trial (mean age 63.6 years) indicated an increased risk of *stroke* and *deep vein thrombosis* in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo. [21]

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

- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
- Estrogens with or without progestins should be prescribed at **the lowest effective dose** for the approved indication.
- Estrogens with or without progestins should be prescribed for the **shortest period possible** for the approved indication.
- The use of pms-Conjugated Estrogens CSD for the prevention of osteoporosis should be considered in light of other available therapies.

### General

**Estrogen Replacement Therapy (ERT) and Hormone Replacement Therapy (HRT) have been associated with increased risks of certain cancers and cardiovascular diseases. The use of unopposed estrogens in women with intact uteri is associated with an increased risk of endometrial cancer.**

**ERT or HRT should not be initiated or continued to prevent cardiovascular disease or dementia.**

**The benefits and risks of ERT and HRT 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 HRT should be assumed to be similar for all estrogens and estrogen/progestin combinations.

**Carcinogenesis and Mutagenesis**

***Breast cancer***

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

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

- 8 more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo). [22]

The WHI study also reported that the invasive breast cancers diagnosed in the *estrogen plus progestin* group were similar in histology but were larger (mean [SD], 1.7 cm [1.1] vs 1.5 cm [0.9], respectively; P=0.04) and were at a more advanced stage compared with those diagnosed in the placebo group. The percentage of women with abnormal mammograms (recommendations for short-interval follow-up, a suspicious abnormality, or highly suggestive of malignancy) was significantly higher in the *estrogen plus progestin* group versus the placebo group. This difference appeared at year one and persisted in each year thereafter. [15]

In the *estrogen-alone* arm of the WHI trial, there was no statistically significant difference in the rate of invasive breast cancer in hysterectomized women treated with conjugated equine estrogens versus women treated with placebo. [21]

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

There is a need for caution in prescribing estrogens for women with known risk factors associated with the development of breast cancer, such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (abnorma1 mammograms and/or atypical hyperplasia at breast biopsy).

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

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

The overall benefits and possible risks of hormone replacement therapy should be fully considered and discussed with patients. It is important that the modest increased risk of being diagnosed with breast cancer after 4 years of treatment with combined estrogen plus

Progestin HRT (as reported in the results of the WHI trial) be discussed with the patient and weighed against its known benefits.

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

**Endometrial hyperplasia & endometrial carcinoma**

Estrogen-only HRT increases the risk of endometrial hyperplasia/carcinoma if taken by women with intact uteri. Estrogen should be prescribed with an appropriate dosage of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma.

The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold or greater than in non-users and appears to be dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five years or more, and this risk has been shown to persist for at least 8 to15 years after ERT is discontinued.

In a subset of WHI (see ACTIONS AND CLINICAL PHARMACOLOGY) no increased risk of endometrial cancer after an average of 5.2 years of treatment with combined estrogen plus progestin HRT compared to placebo was observed.

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur at a rate of approximately 1% or less with CEE or CEE/MPA in two large clinical trials [Health and Osteoporosis, Progestin and Estrogen (n=2,153) and Menopausal Study Group (n=1,385)]. [34,35] In these two clinical trials two cases of endometrial cancer were reported to occur among women taking combination CEE/MPA.

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

***Ovarian cancer***

In some epidemiologic studies, use of estrogen-only products, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. The analysis of the WHI data suggested that estrogen plus progestin therapy may increase the risk of ovarian cancer. Other epidemiologic studies have not found these associations. [18, 19, 25]

**Cardiovascular**

*Cardiovascular risk*
HRT has been associated with an increased risk of cardiovascular events such as myocardial infarction (MI) and stroke, as well as venous thrombosis and pulmonary embolism (PE) (venous thromboembolism or VTE). Should any of these occur or be

suspected, HRT should be discontinued immediately.

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

***General***

The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of *estrogen plus progestin* is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women.[11, 22, 29] The results of the WHI trial indicate that the use of *estrogen-alone and estrogen plus progestin* is associated with an increased risk of stroke in postmenopausal women.[8, 21]

***WHI trial findings***

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

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

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

- 12 more cases of stroke (44 on *estrogen-alone* therapy versus 32 on placebo)
- no statistically significant difference in the rate of CHD. [21]

***HERS and HERS II findings***

In the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with documented heart disease (n=2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg oral medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit. Specifically, during an average follow-up of 4.1 years, treatment with CEE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the hormone-treated group than in the placebo group in year 1, but not during the subsequent years. [11]

From the original HERS trial, 2321 women consented to participate in an open label extension of HERS known as HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD. [29]

***Blood pressure***

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

**Endocrine and Metabolism**

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

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

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

*Heme metabolism*
Women with porphyria need special surveillance.

Estrogens should be used with caution in individuals with severe hypocalcemia.

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

*Hypothyroidism*
Patients who require thyroid hormone replacement therapy and who are also taking estrogen should have their thyroid function monitored regularly to assure that thyroid hormone levels remain in an acceptable range (see ***Drug-Laboratory Test Interactions***).

**Genitourinary**

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

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

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

**Hematologic**

*Venous thromboembolism*

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

In the *estrogen plus progestin* arm of the WHI trial, among 10,000 women on combined HRT over a one-year period, there were 18 more cases of venous thromboembolism, including 8 more cases of pulmonary embolism.[(22)]

In the *estrogen-alone* arm of the WHI trial, among 10,000 women on estrogen therapy over a one-year period, there were 7 more cases of venous thromboembolism, although there was no statistically significant difference in the rate of pulmonary embolism. [(21)]

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

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

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

**Hepatic/Biliary/Pancreatic**

***Gallbladder diseases***

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

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

***Jaundice***
Caution is advised in patients with a history of liver and/or biliary disorders. If cholestatic jaundice develops during treatment, the treatment should be discontinued and appropriate investigations carried out.

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

**Immune**

***Systemic lupus erythematosus***
Particular caution is indicated in women with systemic lupus erythematosus.

**Neurologic**

***Cerebrovascular insufficiency***

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

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

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

The Women's Health Initiative Memory Study (WHIMS), a clinical substudy of the WHI, was designed to assess whether postmenopausal hormone replacement therapy (oral *estrogen plus progestin* or oral *estrogen-alone*) reduces the risk of dementia in women aged 65 and over (age range 65-79 years) and free of dementia at baseline.[12, 27]

In the *estrogen plus progestin* arm of the WHIMS (n=4532), women with intact uteri were treated with daily 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg

medroxyprogesterone acetate (MPA) or placebo for an average of 4.05 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 23 more cases of probable dementia (45 on combined HRT versus 22 on placebo). [12]

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

- 12 more cases of probable dementia (37 on *estrogen-alone* versus 25 on placebo), although this difference did not reach statistical significance. [27]

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

- 18 more cases of probable dementia (41 on *estrogen plus progestin* or *estrogen-alone* versus 23 on placebo). [27]

***Epilepsy***
Particular caution is indicated in women with epilepsy, as estrogens with or without progestins may cause an exacerbation of this condition.

**Ophthalmologic**

*Visual abnormalities*
Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

**Psychiatric**

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

**Renal**

*Fluid retention*
Estrogens may cause fluid retention.

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

**Special Populations**

**Pregnant Women:** Estrogens/progestins should not be used during pregnancy.

**Nursing Women:** Estrogen should not be used during lactation.

**Pediatrics (< 16 years of age):** pms-Conjugated Estrogens CSD is not indicated for use in children.

**Geriatrics (> 65 years of age):** Of the total number of subjects in the conjugated equine estrogens in combination with medroxyprogesterone acetate substudy of the Women's Health Initiative study (WHI), 44% (n=7320) were 65 years and over, while 6.6% (n=1,095) were 75 and over. No significant differences in relative risks were observed between subjects 65 years and over compared to younger subjects. There was a higher relative risk of stroke and invasive breast cancer in women 75 and over compared to younger subjects.

**Monitoring and Laboratory Tests**

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

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

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

## ADVERSE REACTIONS

**Adverse Drug Reaction Overview**

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

The following additional adverse reactions have been reported with estrogen replacement therapy or are undesirable effects associated with hormone replacement therapy:

**Blood and lymphatic system disorders**

Altered coagulation tests (see **WARNINGS AND PRECAUTIONS, *Drug-Laboratory***

***Tests Interactions*).**

**Cardiac disorders**

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

**Endocrine disorders**

Increased blood sugar levels; decreased glucose tolerance, carbohydrate tolerance

**Eye disorders**

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

**Gastrointestinal disorders**

Nausea; vomiting; abdominal discomfort (cramps, pressure, pain), bloating, pancreatitis, gallbladder disorder.

**General disorders and administration site conditions**

Fatigue; changes in appetite; changes in body weight; changes in libido. exacerbation of porphyria, hypocalcemia, exacerbation of asthma, angioedema, anaphylactic/anaphlactoid reactions, increased triglycerides.

**Hepatobiliary disorders**

Gallbladder disorder; cholestatic jaundice; asymptomatic impaired liver function.

**Musculoskeletal and connective tissue disorders**

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

**Nervous system disorders**

Aggravation of migraine episodes; headaches; dizziness; cerebrovascular accident/stroke, exacerbation of epilepsy, stroke, exacerbation of chorea, somnolence, insomnia.

**Psychiatric disorders**

Mental depression; nervousness; irritability, anxiety, mood disturbances, dementia, fatigue.
**Renal and urinary disorders**

Cystitis; dysuria; sodium retention; edema.

**Reproductive system and breast disorders**

Breakthrough bleeding; spotting; change in menstrual flow and abnormal withdrawal bleeding or flow, dysmenorrhea; vaginal itching/discharge; dyspareunia; endometrial hyperplasia; premenstrual-like syndrome; reactivation of endometriosis; changes in cervical erosion and amount of cervical secretion; vaginal candidiasis, amenorrhea, vaginitis, increase in size of uterine leiomyomata, breast swelling and tenderness, breast pain, enlargement, galactorrhea, breast discharge.

**Skin and subcutaneous tissue disorders**

Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; haemorrhagic eruption; loss of scalp hair; hirsutism and acne, urticaria, pruritus, generalized rash, rash (allergic) with without pruritus, alopecia.

**Vascular disorders**

Thrombophlebitis; thromboembolic disorders, venous thrombosis.

**Clinical Trial Adverse Drug Reactions**

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

A phase III double-blind, randomized study was conducted to compare the efficacy and safety of various regimens of conjugated estrogen and medroxyprogesterone acetate (MPA). Efficacy was determined by the incidence of endometrial hyperplasia at the twelve month evaluation. A total of 1,724 generally healthy postmenopausal women (mean age, 54.0 years ± SD 4.6) participated in the study. The patients were considered as having completed the study if they participated in all 13 cycles (28 days/cycle). The five arms in the study were: 2 for conjugated estrogen plus medroxyprogesterone acetate (continuous therapy), 2 for conjugated estrogen plus medroxyprogesterone acetate (cyclic therapy), and 1 for conjugated estrogen alone.

Prior to treatment, the following were performed: physical examinations, vital signs, papanicolaou smear, laboratory safety screen, mammography, follicle stimulating hormone (FSH), and endometrial biopsy. During the patient visit for Cycle 6, all but the mammography and FSH were performed. At the end of the study, Cycle 13, all but the FSH were performed.

No dose-dependent incidence of adverse experiences was seen in the multicenter efficacy

and safety study. Significantly ($p < 0.05$) fewer (12%) conjugated estrogen treated patients reported breast pain than in the conjugated estrogen / MPA groups. Headache was the most common drug-related study event in the conjugated estrogen alone group, reported by 69 (20%) patients. Table 1 summarizes the treatment-emergent drug-related study events reported by 2% or more of the patients.

**Table 1: Treatment-Emergent Drug-Related Study Events With an Incidence of ≥ 2%**

| Study Event | conjugated estrogen 0.625 mg CE (n=347)<br><br>No. (%) Patients + |
|---|---|
| **General disorders and administration site conditions** | |
| Asthenia | 18 (5) |
| Chest pain | 2 (<1) |
| Generalized edema | 9 (3) |
| Edema | 5 (1) |
| Peripheral edema | 11 (3) |
| Pain | 11 (3) |
| **Vascular disorders** | |
| Hypertension | 7 (2) |
| Vasodilatation | 9 (3) |
| **Gastrointestinal disorders** | |
| Diarrhea | 6 (2) |
| Dyspepsia | 4 (1) |
| Flatulence | 14 (4)[b] |
| Nausea | 19 (5) |
| Abdominal pain | 46 (13) |
| **Musculoskeletal connective tissue, and bone disorders** | |
| Leg cramps | 8 (2) |
| Back pain | 13 (4) |
| **Nervous system disorders** | |

| Study Event | conjugated estrogen 0.625 mg CE (n=347)<br><br>No. (%) Patients + |
|---|---|
| Headache | 69 (20) |
| Depression | 22 (6) |
| Migraine | 7 (2) |
| Dizziness | 10 (3) |
| Emotional lability | 4 (1) |
| Insomnia | 2 (<1) |
| Nervousness | 1 (<1)[b,d] |
| **Skin and subcutaneous tissue disorders** | |
| Acne | 6 (2) |
| Pruritus | 6 (2)[a,b] |
| Rash | 5 (1) |
| **Reproductive system and breast disorders** | |
| Breast enlargement | 4 (1)[a,b] |
| Breast pain * | 40 (12)[a,b,d] |
| Cervix disorder ** | 12 (3) |
| Dysmenorrhea | 17 (5)[d] |
| Endometrial hyperplasia | 57 (20) |
| Leukorrhea | 24 (7) |
| Menstrual disorder | 3 (<1) |
| Pelvic pain | 16 (5) |
| Uterine spasm | 0 (0)[a,d] |
| Vaginal bleeding *** | 28 (8)[b] |
| Vaginitis | 4 (1)[a,b] |
| **Investigations** | |
| Pap smear abnormal† | 0 (0)[a] |
| Weight increased | 10 (3) |
| **Psychiatric disorders** | |
| Depression | 22 (6) |
| Emotional lability | 4 (1) |
| Nervousness | 1 (<1)[b,d] |

\+ Patients were counted only once for a particular study event.

* Breast pain also includes breast discomfort, breast soreness, breast tenderness, mastodynia, nipple soreness and nipple tenderness.

** Cervix disorder includes cervical dysplasia, cervical erosion, cervical

hypersecretion.

† Pap smear abnormal refers to positive Pap smear class III through V.

*** Vaginal bleeding includes menorrhagia, metrorrhagia, uterine hemorrhage, and vaginal hemorrhage.

a, b, d, = Significant difference ( $p < 0.05$) from treatment group conjugated estrogen plus medroxyprogesterone acetate (0.625/2.5 mg), conjugated estrogen plus medroxyprogesterone acetate (0.625/5.0 mg), conjugated estrogen plus medroxyprogesterone acetate (0.625/10.0 mg) and conjugated estrogen (0.625 mg) respectively.

The above Table 1 summarizes the treatment-emergent drug-related study events reported by greater than 2% of the patients. The number of patients with any study event is not necessarily the sum of the individual events since a patient might have reported two or more different study events. The addition of progestin to estrogen replacement therapy may contribute to breast pain. This is reflected by the greater percentage of patients with breast pain on combination therapy than on conjugated estrogen alone.

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

## DRUG INTERACTIONS

### Overview

In vitro and in vivo studies have shown that 17 β-estradiol, one of the components of conjugated estrogens, is metabolized partially by Cytochrome P450 3A4 (CYP3A4). Therefore, strong CYP3A4 inducers such as phenobarbitol, phenytoin, carbamazepine, rifampicin and dexamethasome may reduce plasma concentrations of 17 β-estradiol. This may lead to a decreased effect and/or changes in the uterine bleeding profile. CYP3A4 inhibitors such as cimetidine, erythromycin, ketoconazole, clarithromycin, itraconazole, and ritonavir may increase plasma concentrations of 17 β-estradiol and may result in side effects.

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

Estrogens may diminish the effectiveness of anticoagulant, antidiabetic and antihypertensive agents.

Preparations inducing liver enzymes (e.g. barbiturates, hydantoins, carbamazepine, meprobamates, phenylbutazone or rifampicin) may interfere with the activity of orally administered estrogens.

### Drug-Drug Interactions

The following section contains information on drug interactions with ethinyl estradiol-

containing products (specifically, oral contraceptives) that have been reported in the public literature. **It is unknown whether such interactions occur with drug products containing other types of estrogens. Therapeutic monitoring is recommended.**

**Hepatic metabolism:** Interactions can occur with drugs that induce microsomal enzymes which can decrease ethinyl estradiol concentrations (eg., rifampin, barbiturates, phenytoin, carbamazepine, troglitazone).

**Gastrointestinal wall:** Sulfation of ethinyl estradiol has been shown to occur in the gastrointestinal (GI) wall. Therefore, drugs which act as competitive inhibitors for sulfation in the GI wall may increase ethinyl estradiol bioavailability (eg., ascorbic acid, acetaminophen).

**Interference in the metabolism of other drugs:** Ethinyl estradiol may interfere with the metabolism of other drugs by inhibiting hepatic microsomal enzymes or by inducing hepatic drug conjugation, particularly glucuronidation. Increased plasma concentrations of cyclosporin, prednisolone, and theophylline have been reported with concomitant administration of certain drugs containing ethinyl estradiol (eg., oral contraceptives containing ethinyl estradiol). In addition, products containing ethinyl estradiol may induce the conjugation of other compounds.

Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine, and clofibric acid have been noted when these drugs were administered with certain ethinyl estradiol-containing drug products (eg., oral contraceptives containing ethinyl estradiol).

**Other interactions with ethinyl estradiol:** Coadministration of atorvastatin and certain ethinyl estradiol-containing drug products (eg., oral contraceptives) increase AUC values for ethinyl estradiol by 20 percent.

Clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

**Drug-Food Interactions**

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

A single dose study in healthy, postmenopausal women was conducted to investigate any potential drug interaction when 2 x 0.625 mg conjugated estrogens and 2.5 mg medroxyprogesterone acetate (MPA) tablets were administered immediately following a high-fat breakfast. Administration with food slowed the absorption of the conjugated estrogens, thereby reducing the $C_{max}$ of the various estrogens by 25% to 30%, and increasing MPA $C_{max}$ by 89% and $AUC_{0-\infty}$ by 28%. Thus, food slightly lowered the Cmax, but did not affect the AUC, of the estrogens from a 0.625 mg conjugated estrogens tablet; food significantly increased the $C_{max}$ and AUC of MPA from a 2.5-mg tablet.

**Drug-Herb Interactions**

It was found that some herbal products (e.g., St. John's wort), which are available as over-the-counter (OTC) products, might interfere with steroid metabolism, and therefore alter the efficacy and safety of estrogen/progestin products. Hot flashes and vaginal bleeding have been reported in patients taking estrogen replacement therapy (ERT) and combined estrogen plus progestin therapy (HRT) and St. John's wort. St. John's wort may induce hepatic microsomal enzymes, which theoretically may result in reduced efficacy of ERT and HRT.

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

**Drug-Laboratory Test Interactions**

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

- increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity, increased coagulation factors VII, VIII, IX, X; increased norepinephrine-induced platelet aggregability; decreased antithrombin III;
- impaired glucose tolerance;
- increased serum triglycerides and phospholipids concentration.
- increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone (T4), as measured bycolumn or radioimmunoassay;T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentrationis unaltered.
- other binding proteins may be elevated in serum i.e., corticosteroid binding globulin (CBG), sex-hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively, free or biologically active hormone concentrations are unchanged;

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

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

## DOSAGE AND ADMINISTRATION

**Dosing Considerations**

Use of estrogens alone or in combination with progestins therapy should be limited to the shortest duration consistent with treatment goals and risks for the individual woman.

Patients should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary (see boxed Serious Warnings and Precautions). For women who have intact uteri, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

**Recommended Dose and Dosage Adjustment**

pms-Conjugated Estrogens CSD therapy may be given continuously with no interruption in therapy, or in cyclical regimens (regimens such as 25 days on drug followed by five days off drug) as is medically appropriate on an individualized basis.

Continuous, non-cyclic therapy may be indicated in hysterectomized women or in cases where the signs and symptoms of estrogen deficiency become problematic during the treatment-free interval. In women with an intact uterus, a progestin should be coadministered for a **minimum** of 10, but preferably at least 12 to 14 days per cycle to avoid overstimulation of the endometrium. In addition, progestin should be administered to minimize the occurrence of endometrial hyperplasia. Unexpected or abnormal vaginal bleeding in such patients requires institution of prompt diagnostic measures, such as endometrial biopsy or curettage to rule out the possibility of uterine malignancy. Since progestins are administered to reduce the risk of hyperplastic changes of the endometrium, patients without a uterus do not require a progestin for this purpose.

**Usual Dosage Range**
Menopausal symptoms: 0.625 - 1.25 mg daily, cyclically or continuously as is medically required. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level providing effective control.

Osteoporosis (loss of bone mass): 0.625 mg daily.

Hypoestrogenism due to:
1. Female hypogonadism: 0.3 mg to 0.625 mg daily, administered cyclically (e.g., 3 weeks on and 1 week off) or continuously as required. Doses are adjusted depending on the severity of symptoms and responsiveness of the endometrium.
2. Female castration or primary ovarian failure: 1.25 mg daily, cyclically or continuously as required. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Atrophic Vaginitis: 0.3 mg to 1.25 mg daily depending upon the tissue response of the individual patient. Administer cyclically or continuously as required.

Vulvar Atrophy: 0.3 mg to 1.25 mg daily depending upon the tissue response of the individual patient. Administer cyclically or continuously as required.

**Missed Dose**

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

**Administration**

Oral

pms-Conjugated Estrogens CSD should be prescribed with an appropriate dosage of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma. Progestin therapy is not required as part of hormone replacement therapy in women who have had a previous hysterectomy.

## OVERDOSAGE

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

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

**Treatment of overdose**

There is no specific antidote and further treatment if necessary should be symptomatic. For management of a suspected drug overdose, contact your regional Poison Control Centre.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

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

Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 micrograms of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

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

Conjugated estrogens used in therapy are soluble in water and are well absorbed through the skin, mucous membranes, and the gastrointestinal tract after release from the drug formulation. Some estrogens are excreted in bile; however, they are reabsorbed from the intestine and returned to the liver through the portal venous system. Water-soluble estrogen conjugates are strongly acidic and are ionized in body fluids, which favours excretion through the kidneys since tubular reabsorption is minimal.

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

estradiol cypionate is absorbed over several weeks.

Administered estrogens and their esters are handled within the body essentially the same way as the endogenous hormones.

## Pharmacodynamics

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

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

*Effects on Osteoporosis associated with estrogen deficiency*
For several years following natural or induced menopause, the rate of bone mass decline is accelerated. Conjugated estrogens reduce bone resorption and retard postmenopausal bone loss. Case-control studies have shown a reduction of up to 60% in hip and wrist fractures in women whose estrogen replacement was begun within a few years of menopause. [36] Studies also suggest that estrogen reduces the rate of vertebral fractures. One clinical study [36] demonstrated that even when estrogen was started as late as fifteen years after menopause, further loss of bone mass was prevented, but was not restored to premenopausal levels. The effect on bone mass conservation is sustained only as long as conjugated estrogens therapy is continued.

*Effects on the Endometrium*
The use of unopposed estrogen therapy has been associated with an increased risk of endometrial hyperplasia, a possible precursor of endometrial adenocarcinoma. [38, 39] The results of clinical studies indicate that the addition of a progestin to an estrogen replacement regimen for more than 10 days per cycle reduces the incidence of endometrial hyperplasia and the attendant risk of adenocarcinoma in women with intact uteri. The addition of a progestin into an estrogen replacement regimen has not been shown to interfere with the efficacy of estrogen replacement therapy for its approved indications.
*Effect on bleeding patterns*
With a continuous therapy, several bleeding patterns may occur. These may range from absence of bleeding to irregular bleeding. If bleeding occurs, it is frequently light spotting or moderate bleeding.

## Pharmacokinetics

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

However, pms-CONJUGATED ESTROGENS CSD contains a modified-release formulation of conjugated estrogens that slowly releases estrogens over several hours. Maximum plasma concentrations of the various conjugated and unconjugated estrogens are attained within 4 to 10 hours after dose administration.

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

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

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

Excretion
During this enterohepatic recirculation, estrogens are desulfated and resulfated and undergo degradation through conversion to less active estrogens (estriol and other estrogens), oxidation to nonestrogenic substances (catecholestrogens, which interact with catecholamine metabolism, especially in the central nervous system), and conjugation with glucuronic acids (which are then rapidly excreted in the urine).

**Special Populations and Conditions**

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

## STORAGE AND STABILITY

Store at 15°C – 30°C.
Keep out of reach of children.

## SPECIAL HANDLING INSTRUCTIONS

None required.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

*[Pr]pms-Conjugated Estrogens CSD Tablets are available as:*

0.3 mg (green) oval-shaped sugar coated tablets in bottles of 100;

0.625 mg (red) oval-shaped sugar coated tablets in bottles of 100, 500;

0.9 mg (pink) oval-shaped sugar coated tablets in bottles of 100; and

1.25 mg (yellow) oval-shaped sugar coated tablets in bottles of 100, 500.

**Medicinal Ingredient**: conjugated estrogens (46.0-70.0% sodium estrone sulfate, 18.5-37.5% sodium equilin sulfate, and 6.5-21.0% sodium 17α-dihydroequilin sulfate).

**Non-medicinal ingredients**: acacia, calcium light, candy varnish, carnauba wax, colloidal silicon, microcrystalline cellulose, stearic acid, talc, sucrose, purified water,

- 0.3 mg tablets also contain: titanium dioxide and Opalux green AS-3385.

- 0.625 tablets also contain: Opalux maroon AS-3911.

- 0.9 mg tablets also contain: titanium dioxide and Opalux pink AS-1481

- 1.25 mg tablets also contain: titanium dioxide and Opalux yellow AS-2110

## PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug Substance

Proper name: Conjugated estrogens, C.S.D.

Chemical name: Not applicable

Molecular formula and molecular mass: Not applicable

Structural formula: Not applicable

Description: Conjugated estrogens C.S.D. contains 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. It is a mixture of at least the following estrogens: estrone, equilin, 17α-dihydroequilin, 17 α -estradiol, 17β-dihydroequilin, δ8,9-dehydroestrone, 17β-estradiol, equilenin, 17 α -dihydroequilenin, 17β-dihydroequilenin and as salts of their sulfate esters.

## CLINICAL TRIALS

### Published Studies

***Vasomotor Symptoms***

**The Postmenopausal Estrogen Progestin Interventions (PEPI) Trial** [30] was a randomized clinical trial (RCT) in 875 postmenopausal women ages 45 to 64 years of age. Vasomotor symptoms were evaluated using a self-reported checklist at baseline, at 1 year, and at 3 years. The five treatment groups received either conjugated equine estrogens (CEE) 0.625 mg/day, CEE 0.625 mg/day plus cyclical (12 days per cycle) medroxyprogesterone acetate (MPA) 10 mg, CEE 0.625 mg/day plus MPA 2.5 mg/day, CEE 0.625 mg/day plus cyclical (12 days per cycle) micronized progesterone (MP) 200 mg, or placebo.

Key observations demonstrated that therapy with CEE alone and CEE with MPA and CEE with MP decreased levels of vasomotor symptoms in subjects over 36 months. On average there were no significant differences in symptom levels between each group.

At year 1, the adjusted odds of having higher vasomotor symptoms for continuous CEE with MPA vs. placebo were 0.17 (0.09, 0.32). At year 3, the adjusted odds for continuous CEE with MPA vs. placebo were 0.39 (0.22, 0.69). These reported results are the odds ratios with 95% confidence intervals from generalized Wald tests in parentheses.

***Vasomotor Symptoms and Vaginal Atrophy***

**The Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) Study** [(31)] was an RCT to evaluate the safety and efficacy of lower doses of CEE and MPA in postmenopausal women. The design included a one year basic study to evaluate the efficacy of lower doses of CEE with and without MPA in relieving vasomotor symptoms (VMS) and vulvar and vaginal atrophy (VVA). A total of 2,673 healthy, postmenopausal women 40 to 65 years of age with an intact uterus (mean age of 53.3 years), including a vasomotor symptom efficacy-evaluable population (n=241 at baseline) participated.

Efficacy measures were frequency and severity of daily hot flushes and Papanicolaou smear with vaginal maturation index (VMI) to assess vaginal atrophy.

There were a total of eight treatment arms consisting of the following:
CEE 0.625 mg/day; CEE 0.625 mg/MPA 2.5 mg/day; CEE 0.45 mg/day; CEE 0.45 mg/MPA 2.5 mg/day; CEE 0.45 mg/MPA 1.5 mg/day; CEE 0.3 mg/day; CEE 0.3 mg/MPA 1.5 mg/day; or placebo.

Key observations for VMS: All active treatment groups significantly reduced mean number of hot flushes from baseline by week 1 or 2 ($P<0.01$) and all active treatment groups significantly reduced mean number of hot flushes compared with placebo by week 2 or 3 ($P<0.001$).

Numbers of hot flushes

- For the placebo group, the mean daily number of hot flushes dropped from approximately 10 at week 1, to approximately 5 at week 12, and continuing at approximately 5 to cycle 13.
- For the 0.625 mg CEE/2.5 mg MPA treatment group, the mean daily number of hot flushes decreased from approximately 10 at week 1, to approximately 1 at week 12, dropping to approximately 0.5 at cycle 13. The difference from placebo was significant ($P<0.5$) beginning from week 2 to the end of cycle 13.

Severity of hot flushes
A mild hot flush was rated a 1, a moderate hot flush a 2, and a severe hot flush a 3.

- For the placebo group, the mean daily severity of hot flushes decreased from approximately 2.1 at week 1, to approximately 1.7 at week 12, and continuing at approximately 1.7 to cycle 13.
- The mean daily severity of hot flushes was significantly lower at all cycles in the CEE 0.625 group, compared with the CEE 0.45 group ($P< 05$). By cycle 2, mean severity in the CEE 0.625 group was significantly lower than in the CEE 0.3 group, and this difference continued through cycle 13 ($P<.05$).

Key observations for VVA: All active treatment groups significantly increased the percentage of superficial cells from baseline at cycles 6 and 13 ($P<0.001$) and all active treatment groups significantly increased the percentage of superficial cells compared with placebo at cycles 6 and 13 ($P<0.001$).

***Osteoporosis – Bone Mineral Density***

**The PEPI Trial** [7] was a RCT in 875 postmenopausal women ages 45 to 64 years of age. This study was designed to assess the effects of CEE alone in comparison with CEE and MPA or MP on bone mineral density (BMD) at the spine and the hip as measured by dual-energy x-ray absorptometry (DXA) technology. Its primary measures were BMD scores at baseline, 12 months and 36 months. Five treatment groups received either CEE 0.625 mg/day, CEE 0.625 mg/day plus cyclical (12 days per cycle) MPA 10 mg, CEE 0.625 mg/day plus MPA 2.5 mg/day, CEE 0.625 mg/day plus cyclical (12 days per cycle) MP 200 mg, or placebo.

Key observations: Women in the placebo group lost significant amounts of BMD at both the spine and the hip compared with active treatments by month 12. All active treatment groups produced significant BMD gains at the spine and hip from baseline by month 12 continuing until month 36 compared with losses in the placebo group. At 36 months, the placebo group had lost an average of 1.8% of spine BMD, and 1.7% of hip BMD, while the active treatment groups gained from 3.5% to 5.0% mean total increases in spinal BMD and a mean total increase of 1.7% hip BMD.

**The Women's HOPE Study** [32] evaluated 822 healthy, postmenopausal women (mean age of 51.6 years) with a modified intent-to-treat population (n=695 at baseline) in a 2 year, randomized, double-blind, placebo controlled osteoporosis substudy.

The efficacy measures were changes in BMD of the lumbar spine (L2 to L4) and total hip, BMC of the total body as measured by DXA, and the two biochemical markers of bone turnover, osteocalcin and N-telopeptides of type I collagen.

There were a total of 8 treatment arms consisting of the following: CEE 0.625 mg/day; CEE 0.625 mg/MPA 2.5 mg/day; CEE 0.45 mg/day; CEE 0.45 mg/MPA 2.5 mg/day; CEE 0.45 mg/MPA 1.5 mg/day; CEE 0.3 mg/day; CEE 0.3 mg/MPA 1.5 mg/day; or placebo.

Key observations: Women in the placebo group experienced significant losses ($P<0.001$) in BMD at the spine compared with baseline at the 24 month visit. All dose formulations of CEE and CEE/MPA were effective in preventing bone loss at the spine and hip from baseline ($P<0.001$) and all were effective in reducing bone turnover from baseline ($P<0.001$).

The secondary analysis of the Women's HOPE study [33] defined bone response to treatment. Response was defined as loss of >2%, <2% loss, or greater than or equal to 0% gain of spine or hip BMD from baseline at months 12 and 24.

The key findings were as follows:

- At 24 months, less than 15.5% of women failed to respond to active treatment (losing >2% in spine BMD) compared with 55.2% in the placebo group.
- At 24 months, less than 15% of women failed to respond to active treatment (losing >2% in hip BMD) compared with 36.5% in the placebo group.

Women who responded to treatment had a significantly greater reduction in markers of bone turnover (osteocalcin & N-telopeptides) at 12 months (P<0.0001 & P=0.0018, respectively) and at 24 months for both markers (P<0.0001) than women who did not respond to treatment.

**Efficacy and Safety Studies**

***Study demographics and trial design***

A phase III double-blind, randomized study was conducted to compare the efficacy and safety of various regimens of conjugated estrogen and medroxyprogesterone acetate (MPA). Efficacy was determined by the incidence of endometrial hyperplasia at the twelve month evaluation. Patients in all five treatment groups took 0.625 mg of conjugated estrogen every day of a 28-day cycle; in four groups, they also took MPA (see Table 2 below).

A total of 1,724 generally healthy postmenopausal women between the ages of 43 and 66 years were admitted to the study. They were eligible to participate in the study if they had their last natural menstrual cycle at least 12 months before entering the study (baseline screening). The serum screening follicle-stimulating hormone (FSH) concentrations had to be higher than the lower limit for postmenopausal women for the given laboratory. The women were relatively healthy and had intact reproductive organs.

The study was comprised of five arms: 4 conjugated estrogens and MPA and 1 for conjugated estrogen alone, as indicated below. Each patient was to participate for 13 cycles (28 days/cycle). A total of 1,361 patients completed the study.

**Table 2: Pivotal Treatment Groups**

| | Strengths (mg) | | |
|---|---|---|---|
| Treatment Group | Conjugated Estrogen | MPA | Days of Use/Cycle |
| A | 0.625 | 2.5 | 1-28 |
| B | 0.625 | 5.0 | 1-28 |
| C* | 0.625 | Placebo | 1-14 |
| | 0.625 | 5.0 | 15-28 |
| D* | 0.625 | Placebo | 1-14 |
| | 0.625 | 10.0 | 15-28 |
| E | 0.625 | Placebo | 1-28 |

* results from these two non-commercialized product presentations have not been included in the "Study results" section.

***Study results***

**Effects on the Endometrium**

Table 3 summarizes the incidence of endometrial hyperplasia after one year of treatment with the continuous (28 days/cycle of both the CE and MPA tablets) therapy.

**Table 3: Incidence of Endometrial Hyperplasia after One Year of Treatment**

| | ……Dose Groups…… | | |
|---|---|---|---|
| Patient | Conjugated Estrogen/MPA 0.625 mg/2.5 mg | Conjugated Estrogen/MPA 0.625 mg/5.0 mg | Conjugated Estrogen 0.625 mg |
| Total Number of patients | 279 | 274 | 283 |
| No. (%) of patients with abnormal biopsies | | | |
| · all focal and non-focal hyperplasia | 2 (<1)* | 0(0)* | 57(20) |

* Significant ($p<0.001$) in comparison with conjugated estrogen alone (0.625 mg).
conjugated estrogen 0.625 mg tablets contain 0.625 mg CE per tablet.

Table 4 summarizes the incidence of endometrial hyperplasia after one year of treatment with conjugated estrogen/medroxyprogesterone acetate, cyclic therapy (MPA tablets taken concomitantly with conjugated estrogen tablets only on days 15 to 28).

**Table 4: Incidence of Endometrial Hyperplasia after One Year of Treatment**

| | ……Dose Groups…… | |
|---|---|---|
| Patient | Conjugated Estrogen/MPA 0.625 mg/10 mg | Conjugated Estrogen 0.625 mg |
| Total Number of patients | 272 | 283 |
| No. (%) of patients with abnormal biopsies | | |
| · all focal and non-focal hyperplasia | 0(0)* | 57(20) |

* Significant ($p<0.001$) in comparison with Conjugated Estrogens CSD alone (0.625 mg).

Women treated with conjugated estrogen and MPA had a significantly ($p < 0.001$) lower incidence of endometrial hyperplasia than women treated with conjugated estrogen alone.

## Effect on bleeding patterns:

Table 5 presents the incidence of amenorrhea for cycles 7 through 13, of the patient group who completed the study with a continuous regimen of conjugated estrogen 0.625 mg alone.

**Table 5: Incidence of Amenorrhea for Cycles 7 through 13**

Percent (Number/Total Number) of Patients

| | …….Dose Groups……. |
|---|---|
| Population | Conjugated Estrogen 0.625 mg |
| Completed 13 cycles | 53.8% (98/182) |

**Withdrawals from the clinical study:**

Safety-related events were the most common primary reasons for withdrawal from the clinical study except in the group treated with conjugated estrogen 0.625 mg CE/10 mg MPA, in which patient request predominated. The reasons for patient withdrawal and the number of patients withdrawn for each of these reasons are shown in Table 6 below.

Table 6: Summary of reasons for withdrawals from clinical study

| Study Drug | # patients | ……Number of Patients (%)……. Safety-Related Reasons | Failed to Return | Other Medical Event | Other Non-medical Event | Patient Request | Prestudy Screen of Protocol Violation | Lack of Efficacy[a] |
|---|---|---|---|---|---|---|---|---|
| 0.625 mg for 28 days in each group: | | | | | | | | |
| 2.5 mg MPA/28 days | 340 | 20 (6) | 6 (2) | 5 (1) | 5 (1) | 12 (4) | 10 (3) | 1 (<1) |
| 5.0 mg MPA/28 days | 338 | 19 (6) | 8 (2) | 8 (2) | 4 (1) | 10 (3) | 10 (3) | 2 (<1) |
| 10 mg MPA/14 days | 348 | 24 (7) | 6 (2) | 8 (2) | 7 (2) | 27 (8) | 6 (2) | 1 (<1) |
| No MPA | 347 | 42 (12) | 6 (2) | 14 (4) | 1 (<1) | 15 (4) | 14 (4) | 0 |

a: Interpreted by the investigator as lack of symptom control

## DETAILED PHARMACOLOGY

See "Action and Clinical Pharmacology" section under the Health Professional Information Section.

## TOXICOLOGY

Acute toxicity studies have been conducted with conjugated estrogens (Conjugated Estrogens CSD).

***Acute Toxicity***

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

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## IMPORTANT: PLEASE READ

**PART III: CONSUMER INFORMATION**

**pms-Conjugated Estrogens CSD**
**(Conjugated estrogens tablets CSD)**
**0.3 mg, 0.625 mg, 0.9 mg, and 1.25 mg**

## IMPORTANT PLEASE READ

This leaflet is part III of a three-part "Product Monograph" published when pms-Conjugated Estrogens CSD was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about pms-Conjugated Estrogens CSD. Contact your doctor or pharmacist if you have any questions about the drug.

### ABOUT THIS MEDICATION

**What the medication is used for:**

- To relieve menopausal and post-menopausal symptoms (vasomotor symptoms like hot flushes and night sweats).
- To prevent osteoporosis caused by low estrogen levels associated with menopause. Osteoporosis is a thinning of the bones that makes them weaker and easier to break.
- To treat certain types of abnormal uterine bleeding due to hormonal imbalance when your doctor has found no serious cause of the bleeding.
- To treat vulva and vaginal atrophy associated with menopause (itching, burning, dryness in or around the vagina, difficulty or burning on urination).

pms-Conjugated Estrogens CSD tablets for the prevention of osteoporosis is recommended only for women who are at risk of developing this condition. Talk to your doctor about whether a different treatment or medicine without estrogens might be better for you.

Adequate diet, calcium and vitamin D intake, cessation of smoking as well as regular weight-bearing exercise should be discussed with your doctor or pharmacist in addition to taking pms-Conjugated Estrogens CSD.

If you use pms-Conjugated Estrogens CSD tablets only to treat symptoms of vulvar and vaginal atrophy associated with menopause, talk with your healthcare provider about whether a vaginal (topical) treatment might be better for you.

pms-Conjugated Estrogens CSD Tablets should not be used by women with intact uteri unless it is prescribed in association with a progestin.

pms-Conjugated Estrogens CSD should be used only under the supervision of a doctor, with regular follow-up at least once a year to identify side effects associated with its use.

Your first follow-up visit should be within 3 to 6 months of starting treatment. Your visit may include a blood pressure check, a breast exam, a Pap smear and pelvic exam. You should have a mammogram before starting treatment and at regular intervals as recommended by your doctor. Your doctor may recommend some blood tests.

You should carefully discuss the risks and benefits of hormone replacement therapy (HRT) with your doctor. You should regularly talk with your doctor about whether you still need treatment with HRT.

**What it does:**

When taking pms-Conjugated Estrogens CSD women are using a hormone, estrogen (i.e. conjugated equine estrogen tablets). pms-Conjugated Estrogens CSD replaces estrogen in your body, which naturally decreases at menopause.

Estrogens are female hormones that are produced by a woman's ovaries and are necessary for normal sexual development and the regulation of menstrual periods during the childbearing years.

When a woman is between the ages of 45 and 55, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels and marks the beginning of menopause (the end of monthly menstrual periods). A sudden drop in estrogen levels also occurs if both ovaries are removed during an operation before natural menopause takes place. This is referred to as surgical menopause.

When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes"). In some women the symptoms are mild; in others they can be severe. These symptoms may last only a few months or longer. Taking pms-Conjugated Estrogens CSD can alleviate these symptoms. If you are not taking estrogen for other reasons, such as the prevention of osteoporosis, you should take pms-Conjugated Estrogens CSD only as long as you need it for relief from your menopausal symptoms.

After menopause, some women develop osteoporosis. This is a thinning of the bones that makes them weaker and allows them to break more easily, often leading to fractures of the vertebrae, hip and wrist bones.

Using pms-Conjugated Estrogens CSD Tablets, in addition to taking adequate calcium (1000 milligrams to 1500 milligrams per day) and vitamin D, and regular weight-bearing exercise, slows down bone thinning and may prevent bones from breaking.

**When it should not be used:**

Before using pms-Conjugated Estrogens CSD be sure to tell your doctor if you have any of the following medical problems, as pms-Conjugated Estrogens CSD should not be used under these conditions:

- **Known, suspected, or past history of breast cancer.**
- **Known or suspected hormone-dependent cancer.**
- Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or had cancer, talk with your healthcare provider about whether you should take pms-Conjugated Estrogens CSD.
- **Unexpected or unusual vaginal bleeding**
- **Have (or have had) blood clot disorders, including blood clots in the legs or lungs or thrombophlebitis (inflammation of the veins).**
- **Serious liver disease**
- **Active or past history of heart disease, heart attacks or stroke.**
- **If you are allergic to pms-Conjugated Estrogens CSD or any of its ingredients, or have had any unusual reactions to its ingredients (see What the medicinal ingredients are and What the nonmedicinal ingredients are).**
- **If you are pregnant or suspect you may be pregnant.** Since pregnancy may be possible early in the pre-menopause while you are still having spontaneous periods, the use of non-hormonal birth control should be discussed with your physician at this time. If you accidentally take estrogen during pregnancy, there is a small risk of your unborn child having birth defects.
- If you have partially or completely lost vision due to blood vessel disease of the eye.
- If you have overgrowth of the lining of the uterus.

**What the medicinal ingredient is:**

Conjugated estrogens

**What the nonmedicinal ingredients are:**
(alphabetically): acacia, calcium light, candy varnish, carnauba wax, colloidal silicon, microcrystalline cellulose, stearic acid, talc, sucrose, purified water.

- 0.3 mg (green) also contain: titanium dioxide and Opalux green AS-3385.
- 0.625 mg (red) also contains: Opalux maroon AS-3911.
- 0.9 mg (pink) also contains: titanium dioxide and Opalux pink AS-1481.
- 1.25 mg (yellow) also contains: titanium dioxide and Opalux yellow AS-2110.

**What dosage forms it comes in:**

**Tablets:** 0.3 mg (green), 0.625 mg (red), 0.9 mg (pink) and 1.25 mg (yellow)

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

The Women's Health Initiative (WHI) is a large clinical study that assessed the benefits and risks of oral combined estrogen plus progestin therapy and oral *estrogen-alone* therapy compared with placebo (a pill with no active ingredients) in postmenopausal women.

The WHI trial indicated an increased risk of myocardial infarction (heart attack), stroke, breast cancer, pulmonary emboli (blood clots in the lungs) and deep vein thrombosis (blood clots in the large veins) in postmenopausal women taking oral combined *estrogen plus progestin*.

The WHI trial indicated an increased risk of stroke and deep vein thrombosis in postmenopausal women with prior hysterectomy (surgical removal of the uterus) taking oral *estrogen-alone*.

Therefore, you should highly consider the following:

- There is an increased risk of developing invasive breast cancer, heart attack, stroke and blood clots in both lungs and large veins with the use of estrogen plus progestin therapy.
- There is an increased risk of stroke and blood clots in the large veins with the use of estrogen-alone therapy.
- Estrogens with or without progestins should not be used for the prevention of heart disease or stroke.
- Estrogens with or without progestins should be used at the **lowest effective dose** and for **the shortest period of time** possible. Regular medical follow-up is advised.

**Breast Cancer**
The results of the WHI trial indicated an increased risk of breast cancer in postmenopausal women taking combined estrogen plus progestin compared to women taking placebo.

The results of the WHI trial indicated no difference in the risk of breast cancer in post-menopausal women with prior hysterectomy taking estrogen-alone compared to women taking placebo.

Estrogens should not be taken by women who have a personal history of breast cancer.

In addition, women with a family history of breast cancer or women with a history of breast lumps, breast biopsies or abnormal mammograms (breast x-rays) should consult with their doctor before starting HRT.

Women should have a mammogram before starting HRT and at regular intervals during treatment as recommended by their doctor.

Regular breast examinations by a doctor and regular breast self-examination are recommended for all women. You should review technique for breast self-examination with your doctor.

**Overgrowth of the lining of the uterus and cancer of the uterus**
The use of estrogen-alone therapy by post-menopausal women who still have a uterus increases the risk of developing endometrial hyperplasia (overgrowth of the lining of the uterus), which increases the risk of endometrial cancer (cancer of the lining of the uterus).

If you still have your uterus, you should take a progestin medication (another hormone drug) regularly for a certain number of days of each month to reduce the risk of endometrial hyperplasia.

You should discuss progestin therapy and risk factors for endometrial hyperplasia and endometrial carcinoma with you doctor. You should also report any unexpected or unusual vaginal bleeding to your doctor.

If you have had your uterus removed, you are not at risk of developing endometrial hyperplasia or endometrial carcinoma. Progestin therapy is therefore not generally required in women who have had a hysterectomy.

**Heart Disease and Stroke**
The results of the WHI trial indicated an increased risk of stroke and coronary heart disease in post-menopausal women taking combined estrogen plus progestin compared to women taking placebo.

The results of the WHI trial indicated an increased risk of stroke, but no difference in the risk of coronary heart disease in post-menopausal women with prior hysterectomy taking estrogen-alone compared to women taking placebo.

**Abnormal Blood Clotting**
The results of the WHI trial indicated an increased risk of blood clots in the lungs and large veins in post-menopausal women taking combined estrogen plus progestin compared to women taking placebo.

The results of the WHI trial indicated an increased risk of blood clots in the large veins, but no difference in the risk of blood clots in the lungs in post-menopausal women with prior hysterectomy taking estrogen-alone compared to women taking placebo.

The risk of blood clots also increases with age, if you or a family member has had blood clots, if you smoke or if you are severely overweight. The risk of blood clots is also temporarily increased if you are immobilized for long periods of time and following major surgery. You should discuss risk factors for blood clots with your doctor since blood clots can be life-threatening or cause serious disability.

**Galbladder Disease**
The use of estrogens by postmenopausal women has been associated with an increased risk of gallbladder disease requiring surgery.

**Dementia**
The Women's Health Initiative Memory Study (WHIMS) was a substudy of the WHI trial and indicated an increased risk of dementia (loss of memory and intellectual function) in post-menopausal women age 65 and over taking oral combined estrogen plus progestin compared to women taking placebo.

The WHIMS indicated no difference in the risk of dementia in post-menopausal women age 65 and over with prior hysterectomy taking oral estrogen-alone compared to women taking placebo.

**BEFORE you use pms-Conjugated Estrogens CSD talk to your doctor or pharmacist if you:**

- have a history of allergy or intolerance to any medications or other substances
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer
- have experienced any unusual or undiagnosed vaginal bleeding
- have a history of uterine fibroids or endometriosis
- have a history of liver disease, liver tumors, or jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy
- have a history of migraine headache
- have a history of high blood pressure
- have a personal or family history of blood clots, or a personal history of heart disease or stroke
- have a history of kidney disease, asthma or epilepsy (seizures)
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
- have been diagnosed with diabetes
- have been diagnosed with porphyria (a disease of blood pigment)
- have a history of high cholesterol or high triglycerides
- are pregnant or may be pregnant
- have had a hysterectomy (surgical removal of the uterus)
- smoke

Other existing conditions you should discuss with your health professional include lupus, very low calcium levels, thyroid problems, fluid retention, gallbladder disease, depression, and breastfeeding. If you have upcoming surgery or prolonged bedrest, you should also discuss these.

## INTERACTIONS WITH THIS MEDICATION

INTERACTIONS WITH THIS MEDICATION
Tell your doctor or pharmacist if you are taking any other medications, including prescription medications, over-the-counter medications, vitamins or herbal products (such as St. John's wort). Some medications (such as medications for high blood pressure, diabetes, blood clots, sleeping, anxiety, seizures, pain-relief and tuberculosis) may affect how pms-Conjugated Estrogens CSD works. pms-Conjugated Estrogens CSD may also affect how other medicines work.

## PROPER USE OF THIS MEDICATION

**Usual dose:**
You should follow the dosage regimen prescribed by your healthcare provider.

Estrogens should be used at the lowest dose possible for your treatment only as long as needed. You and your healthcare provider should talk regularly (for example every 3 to 6 months) about the dose you are taking and whether you still need

treatment with pms-Conjugated Estrogens CSD.

Do not give pms-Conjugated Estrogens CSD to other people, even if they have the same symptoms you have. It may harm them.

**Overdose:**
Contact your physician or local Poison Control Center in case of accidental ingestion of high doses of pms-Conjugated Estrogens CSD.

Overdosage with estrogens may cause nausea and vomiting, breast discomfort, fluid retention, bloating or vaginal bleeding may occur in women. There is no specific antidote and further treatment if necessary should be symptomatic.

Overdosage may result in a period of amenorrhea (lack of menses) of a variable length and may be followed by irregular menses for several cycles. No cases of overdosage in male patients have been reported.

**Missed Dose:**
If you miss a dose, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your normal schedule. Do not take 2 doses at the same time.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

**Possible side effects include:**

| | |
|---|---|
| Common<br>≥ 1% and < 10% | Breast pain; Breakthrough bleeding; spotting; joint pain; hair loss, change in weight (increase or decrease) |
| Uncommon<br>≥ 0.1% and <1% | Change in menstrual flow; nausea; bloating; abdominal pain; dizziness; headache (including migraine); changes in libido; mood disturbances; rash; itching; inflammation of the vagina |
| Rare<br>≥ 0.01% and < 0.1% | A spontaneous flow of milk from the nipple; painful periods; vomiting; irritability; hives; worsening of asthma |
| Very Rare < 0.01% | Tender red nodules on the shins and legs; increase in blood pressure. |

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

| Frequency (common or uncommon) | Symptom / possible side effect | Talk with your doctor or pharmacist | | Stop taking drug and call your doctor or pharmacist |
|---|---|---|---|---|
| | | Only if severe | In all cases | |
| Common | Breast lump, unusual discharge. | | √ | |
| | Pain or swelling in the leg. | | | √ |
| | Unexpected vaginal bleeding. | | √ | |
| Uncommon | Abdominal pain, nausea or vomiting | √ | | |
| | Persistent sad mood | | √ | |

| | | | | |
|---|---|---|---|---|
| Rare | Shortness of breath, weakness, unusual fatigue, cold sweat, dizziness, sleep disturbance, indigestion, anxiety | | √ | |
| | Sharp pain in the chest, coughing blood or sudden shortness of breath | | | √ |
| | Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech ore weakness or numbness in an arm or leg | | | √ |
| | Crushing chest pain or chest heaviness | | | √ |
| Very rare | Sudden partial or complete loss of vision | | | √ |
| | Yellowing of the skin or eyes | | | √ |

*This is not a complete list of side effects. If you have any unexpected effects while taking this drug, contact your doctor or pharmacist.*

## HOW TO STORE IT

Store pms-Conjugated Estrogens CSD at 15º C and 30º C (room temperature).
Keep out of reach of children.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  -Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

***NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.***

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting Pharmascience Inc., at 1-888-550-6060.

This leaflet was prepared by Pharmascience Inc.

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