PRODUCT MONOGRAPH

PrC.E.S.®

(conjugated estrogens tablets, CSD)

0.3 mg, 0.625 mg, 0.9 mg, and 1.25 mg

Estrogen

Valeant Canada limitée/Limited
4787 Levy Street
Montreal, Quebec
H4R 2P9

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Pr C.E.S.®

Conjugated estrogens

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets / 0.3 mg, 0.625 mg, 0.9 mg, and 1.25 mg	*Lactose (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism,** under **Other conditions).*** *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

C.E.S.® (conjugated estrogens tablets, CSD) is indicated for:

In female patients:

- Relief of menopausal and postmenopausal symptoms occurring in naturally or surgically induced estrogen deficiency states including vaginal and vulvar atrophy (with or without pruritus). **When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.**
- Prevention and treatment of osteoporosis in naturally occurring or surgically induced estrogen-deficiency states. This is in addition to other important therapeutic measures such as adequate diet, calcium and vitamin D intake, cessation of smoking, as well as regular physical weight bearing exercise. C.E.S.® for prevention and treatment of osteoporosis is to be considered in light of other available therapies (see **Boxed Warnings**).
- Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.
- Atrophic vaginitis.

In patients with intact uteri, C.E.S.® should always be supplemented by administration of a progestin whose role is to prevent endometrial hyperplasia/carcinoma.

In male patients:

- Inoperable progressing prostatic cancer (for palliation only when castration is not feasible, or when castration failed or delayed escape following a response to castration occurred).

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

Pediatrics (< 16 years of age): C.E.S.® is not indicated for use in children.

CONTRAINDICATIONS

Treatment with C.E.S.® (conjugated estrogens) is contraindicated in 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 arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease).
- Active or past history of confirmed venous thromboembolism (such as deep vein thrombosis or pulmonary embolism) or active thrombophlebitis.
- Partial or complete loss of vision due to ophthalmic vascular disease.
- During breastfeeding since estrogens pass into breast milk.
- Classical migraine.

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.[1-3]

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.[1]

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.[2]

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 C.E.S.® for the prevention or treatment of osteoporosis should be considered in light of other available therapies.

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).[1]

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.[3]

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.[2]

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 (abnormal 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 and 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.

Ovarian cancer
Some recent epidemiologic studies have found that the use of hormone replacement therapy (estrogen-alone and estrogen plus progestin therapies), in particular for five or more years, has been associated with an increased risk of ovarian cancer.

Cardiovascular
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.[1,4,5]
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.[1,2]

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).[1]

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.[2]

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.[4]

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.[5]

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.

Ear/Nose/Throat
Otosclerosis
Estrogens should be used with caution in patients with otosclerosis.

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.

Heme metabolism
Women with porphyria need special surveillance.

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**).

Other conditions
C.E.S.® contains lactose. In patients with rare hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption, the severity of the condition should be taken into careful consideration before prescribing C.E.S.®. The patients should be closely monitored.

Genitourinary
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.

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.

Endometriosis
Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use.

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.[1]

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.[2]

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

Hepatic hemangioma

Particular caution is indicated in women with hepatic hemangiomas as estrogens 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 the section under **Monitoring and Laboratory Tests**.

Immune

Angioedema

Estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema.

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.

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.[6,7]

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).[6]

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.[7]

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).[7]

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

Peri-Operative Considerations
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.

Renal
Fluid retention
Estrogens may cause fluid retention. Therefore, particular caution is indicated in cardiac or 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: Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive-tract disorders. In females there is an increased risk of vaginal adenosis, squamous cell dysplasia of the cervix, and cancer later in life; in the male, of urogenital abnormalities. Although some of these changes are benign, it is not known whether they are precursors of malignancy (see **CONTRAINDICATIONS**).

Nursing women: Estrogens should not be used during breastfeeding since they pass into breast milk (see **CONTRAINDICATIONS**).

Monitoring and Laboratory Tests
Before C.E.S® (conjugated estrogens) 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.

The first follow-up examination should be done within 3-6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the physician.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview
See **Warnings and Precautions** regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

The following adverse reactions have been reported with estrogen/progestin combination in general:

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.

Endocrine disorders
Increased blood sugar levels; decreased glucose tolerance.

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

Gastrointestinal disorders
Nausea; vomiting; abdominal discomfort (cramps, pressure, pain, bloating).

General disorders and administration site conditions
Fatigue; changes in appetite; changes in body weight; changes in libido.

Hepatobiliary disorders
Gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice.

Musculoskeletal and connective tissue disorders
Musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur.

Nervous system disorders
Aggravation of migraine episodes; headaches; dizziness; neuritis.

Psychiatric disorders
Mental depression; nervousness; irritability.

Renal and urinary disorders
Cystitis; dysuria; sodium retention; edema.

Reproductive system and breast disorders
Breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea ; vaginal itching/discharge; dyspareunia ; endometrial hyperplasia; pre-menstrual-like syndrome; reactivation of endometriosis; changes in cervical erosion and amount of cervical secretion; breast swelling and tenderness.

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.

Vascular disorders
Isolated cases of: thrombophlebitis; thromboembolic disorders.

Clinical Trial Adverse Drug Reactions
Data are not available.

Less Common Clinical Trial Adverse Drug Reactions
Data are not available.

Abnormal Hematologic and Clinical Chemistry Findings
Data are not available.

Post-market Adverse Drugs Reactions
The following post-marketing adverse drug reactions have been reported for C.E.S.:

Cardiovascular Disorders
Myocardial infarction, increase blood pressure, palpitation

Gastrointestinal Disorders
Abdominal pain, bloating, dyspepsia, nausea, vomiting, diarrhoea, gallbladder disorder

General disorders and administration site conditions
Allergic reaction, headache, hot flushes, lack of drug effect, sweating, weight increase, chills, fatigue, dizziness, feeling strange, pain

Eye disorders
Dry eyes

Musculoskeletal and connective tissue disorders
Arthralgia, muscle cramp, pain legs, bursitis, arthritis aggravated

Neoplasm benign, malignant and unspecified (incl cysts and polyps)
Breast cancer

Nervous system disorders
Cerebral infarction, stroke, muscle weakness, swallowing difficult, facial palsy, abnormal coordination, memory impairment

Psychiatric disorders
Anger, anxiety, insomnia, depression, irritability, thinking abnormal, impaired concentration

Reproductive System and breast disorders
Postmenopausal bleeding, uterine hemorrhage, breast tenderness, menstrual disorders, atrophic vaginitis, menorrhagia

Skin and subcutaneous tissue disorders
Chloasma, skin hyperpigmentation, papular rash, rash, urticaria, pruritus, dermatitis

Vascular Disorders
Venous deep thrombosis

Others
Antinuclear factor test positive

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

DRUG INTERACTIONS

Overview
Estrogens may diminish the effectiveness of anticoagulants, 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.

1. The metabolism of ethinyl estradiol is increased by rifampin and anticonvulsants such as phenobarbital, phenytoin and carbamazepine. Coadministration of troglitazone and certain ethinyl estradiol containing drug products (e.g., oral contraceptives containing ethinyl estradiol) reduce the plasma concentrations of ethinyl estradiol by 30 %.

   Ascorbic acid and acetaminophen may increase AUC and/or plasma concentrations of ethinyl estradiol. Coadministration of atorvastatin and certain ethinyl estradiol containing drug products (e.g., oral contraceptives containing ethinyl estradiol) increase AUC values for ethinyl estradiol by 20%.

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

2. Drug products containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporin, prednisolone, and theophylline have been reported with concomitant administration of certain drugs containing ethinyl estradiol (e.g., oral contraceptives containing ethinyl estradiol). In addition, these drugs 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 (e.g., oral contraceptives containing ethinyl estradiol).

Drug-Food Interactions
As other inhibitors of CYP3A4, grapefruit juice may increase plasma concentration of 17 ß-estradiol, possibly resulting in side effects.

Drug-Herb Interactions
It was found that some herbal products (e.g. St. John's wort) which are available as over-the-counter (OTC) products might interfere with steroid metabolism and therefore, alter the efficacy and safety of estrogen/progestin products.

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

- increased thyroxine-binding globulin (TBG), leading to increased circulating total thyroid hormone (T_4) as measured by column or radioimmunoassay; T_3 resin uptake is decreased, reflecting the elevated TBG; free T_4 concentration is 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;

- impaired glucose tolerance;

- increased serum triglycerides and phospholipids concentration;

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.

Drug-Lifestyle Interactions
Acute alcohol ingestion during HRT may lead to elevations in circulating estradiol levels.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Conjugated estrogens therapy may be given continuously with no interruption in therapy, or in cyclical regimens (regimens such as 25 days on drug followed by 5 days off drug) as is medically appropriate on an individualized basis.

Continuous, noncyclic 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 days, 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 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.

Recommended Dose and Dosage Adjustment
Usual Dosage Range

Menopausal symptoms: 0.625 to 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 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

C.E.S.® 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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms:
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. Over dosage with estrogen may cause nausea, breast discomfort, fluid retention, bloating or vaginal bleeding in women.

Treatment:
Symptomatic treatment should be given.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Conjugated estrogens are a mixture of estrogens derived from plant sterols and contain the sodium salts of water-soluble estrogen sulfates. C.E.S.® (conjugated estrogens) is derived from plant sterols only. Conjugated estrogens contain estrone, equilin, 17-α-dihydroequilin, 17-α-estradiol, equilenin and 17-α-dihydroequilenin as salts of their sulfate esters.

Estrogen drug products act by regulating the transcription of a limited number of genes. They may act directly at the cell's surface via non-"estrogen receptor" mechanism or directly with the estrogen receptor inside the cell. Estrogens diffuse through cell membranes, distribute

themselves throughout the cell, bind to and activate the nuclear estrogen receptor, a DNA-binding protein found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, which enhance the transcription of adjacent genes and in turn lead to the observed effects. Estrogen receptors have been identified in the wall of blood vessels, in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone of women.

Estrogens are important in 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. Together 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 involved together with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy, and affect the release of pituitary gonadotropins. They also contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, and pigmentation of the nipples and genitals.

Pharmacodynamics

Conjugated estrogens used in therapeutic preparations are soluble in water and are well absorbed from the gastrointestinal tract after release from the drug formulation.

Estrogen deficiency and vasomotor symptoms:

As a result of the decrease in ovarian hormones, about 75 % of menopausal women experience vasomotor symptoms such as hot flushes and sweating, and these symptoms are seen whether menopause is surgically induced or spontaneous. Vasomotor symptoms may begin before the cessation of menses.

Estrogen deficiency and Osteoporosis:

The rate of bone mass decline is accelerated for several years following natural or induced menopause. Conjugated estrogens reduce postmenopausal bone loss. Up to 60% reduction in hip and wrist fractures in women given estrogen within a few years of menopause has been documented in case-control studies.[12] Other studies suggest that estrogen reduces the rate of vertebral fractures.[13]

In postmenopausal women already diagnosed as having osteoporosis and vertebral fractures, treatment with conjugated estrogens may prevent further loss of bone mass. Even when started as late as six years after menopause, estrogen prevents further loss of bone mass for as long as the treatment is continued. When estrogen therapy is discontinued, bone mass declines at a rate comparable to that of the immediate postmenopausal period.

Effects on the Endometrium

An increased risk of endometrial hyperplasia, a possible precursor of endometrial adenocarcinoma, has been associated with the use of unopposed estrogen therapy.[14,15] The results of clinical studies indicate that the addition of a progestin to an estrogen replacement regimen

reduces the incidence of endometrial hyperplasia and the attendant risk of adenocarcinoma in women with intact uteri without interfering with the efficacy of estrogen replacement therapy for its approved indications.

Effect on bleeding patterns
With a continuous therapy, bleeding patterns such as absence of bleeding to irregular bleeding, may occur. However, it is frequently light spotting or moderate bleeding.

Pharmacokinetics

Absorption:
Conjugated estrogens used in therapeutic preparations are soluble in water and are well absorbed from the gastrointestinal tract after release from the drug formulation.

Distribution:
Administered estrogens and their esters are handled within the body essentially the same way as the endogenous hormones. Metabolic conversion of estrogen 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 nonesterified forms. Although naturally occurring estrogens circulate in the blood largely bound to sex hormone-binding globulin (SHBG) and albumin, only unbound estrogens enter target tissue cells. A significant proportion of the circulating estrogen exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogenic species.

Metabolism:
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:
A certain proportion of the estrogen is excreted into the bile, then reabsorbed from the intestine and returned to the liver through the portal venous system. 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 CNS), 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.

Estrogen Pharmacology

Estrogens occur naturally in several forms. The primary source of estrogen in normally cycling women is the ovarian follicle, which secretes 70 to 500 μg of estradiol daily, depending on the phase of the menstrual cycle. Estradiol is converted primarily to estrone, which circulates in roughly equal proportion to estradiol, and to small amounts of estriol. After menopause, most endogenous estrogen stems from the conversion of androstenedione, which is secreted by the adrenal cortex, to estrone in peripheral tissues.

Thus, estrone, especially in its sulfate ester form, is the most abundant circulating estrogen in postmenopausal women. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estriol at the receptor site.

An increased risk of endometrial hyperplasia, a possible precursor of endometrial adenocarcinoma, has been associated with the use of unopposed estrogen therapy.[14,15] The results of clinical studies indicate that the addition of a progestin to an estrogen replacement regimen reduces the incidence of endometrial hyperplasia and the attendant risk of adenocarcinoma in women with intact uteri without interfering with the efficacy of estrogen replacement therapy for its approved indications.

STORAGE AND STABILITY

Store at room temperature (15-30°C).
Keep out of reach of children.

SPECIAL HANDLING INSTRUCTIONS

None required.

DOSAGE FORMS, COMPOSITION AND PACKAGING

C.E.S. tablets for oral administration are available as:

C.E.S.® 0.3 mg: Each oval, green sugar-coated tablet contains 0.3 mg conjugated estrogens, CSD, calcium carbonate, calcium sulphate, carnauba wax, D&C yellow No. 10, FD&C blue No. 1, FD&C blue No. 2, FD&C yellow No. 6, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, magnesium stearate, methylparaben, microcrystalline cellulose, povidone, sodium benzoate, sucrose, talc, titanium dioxide and white wax. Bottles of 100.

C.E.S.® 0.625 mg: Each oval, maroon sugar-coated tablet contains 0.625 mg conjugated estrogens, CSD, calcium carbonate, calcium phosphate, calcium sulphate, carnauba wax,

colloidal silicon dioxide, lactose, magnesium carbonate, FD&C blue No. 2, FD&C red No. 40, methylparaben, microcrystalline cellulose, povidone, sodium benzoate, starch, sucrose, talc, titanium dioxide, stearic acid and white wax. Bottles of 100 and 1000.

C.E.S.® 0.9 mg: Each oval, pink sugar-coated tablet contains 0.9 mg conjugated estrogens, CSD, calcium carbonate, calcium sulphate, carnauba wax, erythrosine aluminum lake, hydroxypropyl methyl cellulose, magesium stearate, methylparaben, microcrystalline cellulose, povidone, sodium benzoate, sucrose, talc, titanium dioxide and white wax. Bottles of 100.

C.E.S.® 1.25 mg: Each oval, yellow sugar-coated tablet contains 1.25 mg conjugated estrogens, CSD, acacia, calcium carbonate, calcium phosphate, calcium sulphate, carnauba wax, colloidal silicon dioxide, lactose, magnesium carbonate, D&C yellow No. 10, FD&C yellow No. 6, methylparaben, microcrystalline cellulose, pharmaceutical glaze, starch, sucrose, talc, titanium dioxide, stearic acid and white wax. Bottles of 100.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

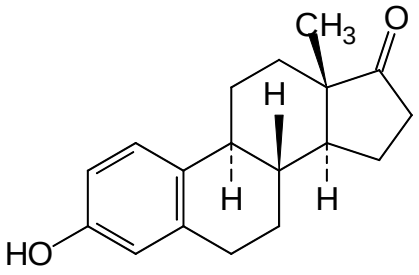
Drug Substance

Proper name: Estrone

Chemical name: Estra-1,3,5(10)-trien-17-one, 3-hydroxy- or 3-Hydroxy-estra-1,3,5(10)-triene- 17-one.

Molecular formula and molecular mass: $C_{18}H_{22}O_2$ 270.37

Structural formula:



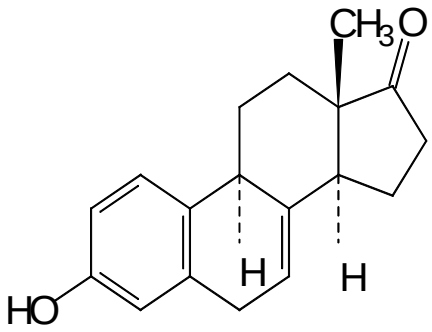
Physicochemical properties: White to light buff, crystalline or amorphous powder; odourless or having a slight odour.

Proper name: Equilin

Chemical name: Estra-1,3,5(10),7-tetraen-17-one,3-hydroxy- or 3-hydroxyestra 1,3,5(10),7-tetraen-17-one.

Molecular formula and molecular mass: $C_{18}H_{20}O_2$ 268.36

Structural formula:



Physicochemical properties: White to light buff, crystalline or amorphous powder; odourless or having a slight odour.

CLINICAL TRIALS

Published Studies

The most relevant safety and efficacy clinical trials with conjugated estrogens reported in the literature are summarized below:

The Post-menopausal Estrogen/Progestin Intervention Trial (PEPI trial) was a 3-year, multicenter, double-blind, placebo-controlled trial in 875 postmenopausal women aged 45-64 years at baseline. Participants were assigned randomly to one of five groups: placebo; conjugated estrogens (CEE) 0.625 mg; CEE 0.625 mg and cyclical medroxyprogesterone (MPA) 10 mg (days 1-12); CEE 0.625 mg and daily MPA 2.5 mg; and CEE 0.625 mg + cyclical micronized progesterone (MP) 200 mg (days 1-12). Symptoms were self-reported using a checklist at 1 and 3 years. Factor analysis reduced 52 symptoms to a set of six symptom groups. At 1 year, each active treatment demonstrated a marked, statistically significant, protective effect against vasomotor symptoms compared with placebo (odds ratios [ORs] 0.17-0.28); there was no additional benefit of estrogen-progestin over estrogen alone. At follow-up year 3 a less pronounced difference between treated and untreated women was observed for vasomotor symptoms level (odds ratios [ORs] 0.26-0.53). Only progestin-containing regimens were significantly associated with higher levels of breast discomfort (OR 1.92-2.27). Anxiety, cognitive, and affective symptoms did not differ by treatment assignment.[18]

To evaluate the frequency of bone loss among women using postmenopausal hormone therapy replicate bone mineral density (BMD) measures of lumbar spine (L2-4), total hip, and hip subregions were done at baseline, 12 months, and 36 months. Five hundreds thirty eight women included in the PEPI trial and adherent to the active treatment were compared with 132 women adherent to placebo. At 12 months, 1.5% of women on the active treatment lost 3% spinal BMD compared with 31.3% of women on the placebo who lost 2.5 % of the spinal BMD; during months 12 to 36, only 0.6% of women on active treatment lost spinal BMD to this degree compared with 11.7% of the women on placebo. For the total hip, during the first 12 months, 2.3% of hormone-adherent women lost -3.0% per year or more, and 32.3% of the placebo-adherent women lost approximately 2.5%. During months 12 to 36, only 0.4% of women in the active treatment group lost 3% or more of the hip BMD compared to 7.9 % of women in the placebo treated group.[19]

The Women's Health Osteoporosis Progestin Estrogen (Women's HOPE) study was a prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial of safety and efficacy of lower-dose regimen of conjugated estrogens (CEE) and medroxyprogesterone (MPA) in postmenopausal women. A total of 2673 healthy postmenopausal women 40 to 65 years with an intact uterus were randomly assigned to one of the eight treatment group (CEE 0.625 mg; CEE 0.625 mg and MPA 2.5 mg; CEE 0.45 mg; CEE 0.45 mg and MPA 2.5 mg; CEE 0.45 mg

and MPA 1.5 mg; CEE 0.3 mg ; CEE 0.3 mg and MPA 1.5 mg; or placebo). Main outcome included vasomotor symptoms, vaginal atrophy, endometrial hyperplasia in the first year and bone mineral density in year two.[20,21]

The efficacy of lower doses of conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) for relieving vasomotor symptoms and vaginal atrophy was evaluated in a subset of 241 symptomatic women following 1 year of treatment. The number and severity of hot flushes and Papanicolaou smear with vaginal maturation index (VMI) assessing the vaginal atrophy, were used as main outcome measures. In the efficacy-evaluable population, reduction in vasomotor symptoms was similar with CEE of 0.625 mg/d and MPA of 2.5 mg/d (the most commonly prescribed doses) and all lower combination doses. CEE of 0.625 mg/d alleviated hot flushes more effectively than the lower doses of CEE alone. VMI improved in all active treatment groups.[20,21]

To evaluate the efficacy of lower doses of CEE/MPA in reducing the incidence of endometrial hyperplasia rates, scheduled endometrial biopsies were performed at baseline and on days 22-28 of cycle 6 and 13. Out of the 2673 patients included in the Women's HOPE study, there were 32 patients who had a diagnosis of endometrial hyperplasia. Twenty-nine of these were in the unopposed estrogen group (CEE 0.625 mg or CEE 0.45 mg alone), and one case of endometrial hyperplasia was identified in each of the CEE 0.45 mg/MPA 1.5 mg, CEE 0.3 mg, and CEE 0.3 mg/MPA 1.5 mg groups. The incidence of hyperplasia increased with age for patients administered CEE alone. One year of treatment with lower doses of CEE/MPA provides endometrial protection comparable to commonly prescribed doses.[22]

Results of the vaginal maturation index showed that lower doses of CEE alone and CEE/MPA were effective in improving the vaginal maturation index in postmenopausal women. The greatest improvement was in the 0.625 group. But all the active treatment groups were significantly improved compared to baseline and placebo.[20,21]

To evaluate the incidence of continued bone loss with lower-dose CEE and CEE/MPA, 822 healthy postmenopausal women included in Women's HOPE study received CEE 0.625 mg; CEE 0.625 mg/MPA 2.5 mg; CEE 0.45 mg; CEE 0.45 mg/MPA 2.5 mg; CEE 0.45 mg/MPA 1.5 mg; CEE 0.3 mg; CEE 0.3 mg/MPA 1.5 mg (all doses in mg/day), or placebo for 2 years along with 600 mg/day of calcium. Changes from baseline in spine and total hip bone mineral density (BMD) were compared among treatment groups in an intent-to-treat analysis. At 12 months, <10% of women on active treatment lost >2% of spinal BMD (except CEE 0.3 mg/MPA 1.5 mg [15.6%]), compared with 41.2% of women on placebo. At 24 months, the percentages of women on active treatment who lost >2% of spine BMD ranged from 4.5% with CEE 0.45 mg/MPA 1.5 mg to 15.6% with CE 0.3 mg/MPA 1.5 mg, compared with 55.2% of women taking placebo. More than 85% of women on active treatment did not experience continued BMD loss at the hip at 12 months and 24 months, in contrast to 30.6% of women on placebo at 12 months and 36.5% at 24 months. [23]

DETAILED PHARMACOLOGY

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

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PART III: CONSUMER INFORMATION

C.E.S.®
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 C.E.S.® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about C.E.S.® Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
C.E.S.® is used to:
- Relieve menopausal and post-menopausal symptoms.
- Help reduce your chances of developing osteoporosis (brittle bones).
- Treat itching, burning, dryness in or around the vagina (atrophic vaginitis).
- Treat vulvar atrophy (changes of the external genitalia associated with low estrogen levels).
- Treat conditions known as "hypogonadism" and "primary ovarian failure" that result in low estrogen secretion early in reproductive life, or to treat the condition of low estrogen levels that follows "castration" (surgical removal of the ovaries).
- Treat inoperable progressing prostatic cancer in male patients.

C.E.S.® should be confined to women who have been diagnosed with osteoporosis or who are at increased risk of developing this condition. If you use C.E.S.® only to prevent osteoporosis associated with menopause, you should talk to your physician 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 C.E.S.®.

If you use C.E.S. ® only to treat symptoms of vulvar atrophy or atrophic vaginitis (itching, burning vagina) associated with menopause, talk with your healthcare provider about whether a vaginal (topical) treatment might be better for you.

C.E.S.® should not be used by women with intact uteri unless prescribed in association with a progestin.

C.E.S.® should only 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 hormones replacement therapy (HRT) with your doctor. You should regularly talk with your doctor about whether you still need treatment with HRT.

What it does:
C.E.S.® (conjugated estrogens) is a medicine that contains a mixture of estrogen hormones. It replaces estrogens 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 flushes"). In some women the symptoms are mild; in others they can be severe. These symptoms may last only a few months or longer. Taking C.E.S.® can alleviate these symptoms but, C.E.S.® should be used for the shortest time possible.

After menopause, same 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 C.E.S.® tablets, in addition to adequate diet, calcium and vitamin D intake, regular weight-bearing exercise, and cessation of smoking, slows down bone thinning and may prevent bones from breaking.

When it should not be used:
Before using C.E.S.® be sure to tell your doctor if you have any of the following medical problems, as C.E.S.® 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 C.E.S.®.
- **Unexpected or unusual genital bleeding.**
- **Have (or have had) blood clot disorders, including blood clots in the legs or lungs.**
- **Have thrombophlebitis (inflammation of the veins).**
- **Serious liver disease.**
- **Active or past history of heart disease, heart attacks or**

stroke.

- **If you are allergic to C.E.S.® or any of its ingredients, or have had any unusual reactions to its ingredients (see What the medicinal ingredients are and What the non-medicinal 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 estrogens 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 (endometriosis).
- Are breast feeding.
- If you have migraine headaches.

What the medicinal ingredient is:
Conjugated estrogens

What the nonmedicinal ingredients are:
Each C.E.S.® Tablet contains the following nonmedicinal ingredients:
Calcium carbonate, calcium sulphate, carnauba wax, methylparaben, microcrystalline cellulose, sucrose, talc, titanium dioxide and white wax.

In addition, the following ingredients are contained in specific strengths as indicated:
Acacia (1.25 mg), calcium phosphate, colloidal silicon dioxide, lactose, magnesium carbonate, starch, stearic acid (0.625 mg & 1.25 mg), D&C yellow N°10 (0.3 mg, 1.25 mg), erythrosine aluminium lake (0.9 mg), FD&C blue N°1 (0.3 mg), FD&C blue N°2 (0.3 mg, 0.625 mg), FD&C yellow N°6 (0.3 mg, 1.25 mg), FD&C Red N°40 (0.625 mg), hydroxypropyl cellulose (0.3 mg), hydroxypropylmethyl cellulose, magnesium stearate (0.3 mg & 0.9 mg), povidone, pharmaceutical glaze (1.25 mg), sodium benzoate (0.3 mg, 0.625 mg & 0.9 mg).

What dosage forms it comes in:
C.E.S.® tablets for oral administration are available as:

- C.E.S.® 0.3 mg: each oval, green sugar coated tablet contains 0.3 mg conjugated estrogens CSD, in bottles of 100;
- C.E.S.® 0.625 mg: each oval, maroon sugar coated tablet contains 0.625 mg conjugated estrogens CSD, in bottles of 100 and 1000;
- C.E.S.® 0.9 mg: each oval, pink sugar coated tablet contains 0.625 mg conjugated estrogens CSD, in bottles of 100; and
- C.E.S.® 1.25 mg: each oval, yellow sugar coated tablet contains 1.25 mg conjugated estrogens CSD, in bottles of 100.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial 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 follow-up is advised.

Breast Cancer
The results of the WHI trial indicated an increased risk of breast cancer in post-menopausal 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 postmenopausal 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-examinations 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 your 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.

Ovarian cancer
In some studies, the use of *estrogen-alone* and *estrogen plus progestin* therapies for 5 or more years has been associated with an increased risk of ovarian cancer.

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.

Gallbladder 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 postmenopausal 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 C.E.S.® 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 tumours, or jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy
• have been told that you have a condition called hereditary angioedema or if you have had episodes of rapid swelling of the hands, feet, face, lips, eyes, tongue, throat (airway blockage), or digestive tract
• have been diagnosed with lupus
• have been diagnosed with hearing loss due to otosclerosis
• 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
• are breastfeeding
• have had a hysterectomy (surgical removal of the uterus)
• smoke

Other existing conditions you should discuss with your health professional include thyroid problems, fluid retention, gallbladder disease, and depression. If you have upcoming surgery or prolonged bed rest, you should also discuss these.

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 C.E.S.® works. C.E.S.® may also affect how other medicines work.

PROPER USE OF THIS MEDICATION

Usual dose:
Take this medicine by mouth (orally) only as directed by your doctor. Do not take more of it and do not take it for a longer period of time than your doctor ordered. The length of time you take the medicine will depend on the medical problem for which you are taking conjugated estrogens. Discuss with your doctor how long you will need to take these medicines.

Nausea may occur during the first few weeks after you start taking estrogens. This effect usually disappears with continued use. If the nausea is bothersome, it can usually be prevented or reduced by taking each dose with food or immediately after food.

Overdose:

For management of a suspected drug overdose, contact your regional Poison Control Centre.

No serious ill effects have been reported following acute ingestion of large doses of estrogens. The following effects have been selected on the basis of their potential clinical significance:

- Nausea or vomiting
- Withdrawal bleeding

Treatment of overdose is symptomatic and patients should consult their physician.

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

All medicines can have side effects. Sometimes they are serious, most of the time, they are not.

Check with your doctor as soon as possible if any of the following occur: abdominal discomfort, indigestion, sleep disturbance, irritability, anxiety, unusual fatigue, cold sweat, swelling of the ankles, fingers or abdomen due to fluid retention (oedema) persisting for more than 6 weeks, change in weight, change in your sex drive, change in vaginal discharge, (may be a sign that too much estrogen is taken), hair loss, excessive hairiness, spotty darkening of the skin particularly on the face or abdomen (chloasma), rash, itching, acne, dryness or discoloration of the skin, purple skin patches, contact lens discomfort.

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

Symptom / 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		✓	
	Pain or swelling in the leg			✓
	Unexpected vaginal bleeding		✓	
	Painful and/or heavy periods		✓	
	Vaginal thrush (vaginal fungal infection with severe itching, vaginal discharge)		✓	
Uncommon	Abdominal pain, nausea or vomiting		✓	
	Persistent sad mood			✓
	Decline of memory or mental ability			✓

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg			✓
	Crushing chest pain or chest heaviness			✓
	Sharp pain in the chest, coughing blood, or sudden shortness of breath			✓
	Intolerable breast tenderness			✓
Very rare	Sudden partial or complete loss of vision			✓
	Yellowing of the skin or eyes (jaundice)			✓

This is not a complete list of side effects. For any unexpected effects while taking C.E.S.®, contact your doctor or pharmacist.

HOW TO STORE IT

- Keep out of reach of children;
- Store at room temperature between (15°-30°C);
- Store away from heat and direct light;
- Do not store in the bathroom, near the kitchen sink, or in other damp places. Heat or moisture may cause the medicine to break down;
- Do not keep outdated medicine or medicine no longer needed. Be sure that any discarded medicine is out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

Online: **www.healthcanada.gc.ca/medeffect**
Toll-freehone: **1-866-234-2345**
Toll-free fax **1-866-678-6789**

Postage Paid Mail:
Canada Vigilance Program
Health Canada
AL 0701C
Ottawa, Ontario K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Valeant Canada limitée/Limited, at:
1-800-361-1448

This leaflet was prepared by Valeant Canada limitée/Limited

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