

PRODUCT MONOGRAPH

 **ESTRACE**[®]

17 β -estradiol Tablets

0.5mg, 1mg, 2mg

Tablets USP

Estrogen

Acerus Pharmaceuticals Corporation
2486 Dunwin Drive
Mississauga, ON
L5L 1J9

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ESTRACE®

(17 β -estradiol Tablets)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 0.5mg, 1mg, 2mg	lactose, tartrazine (2mg tablets only) <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

ESTRACE (17 β -estradiol Tablets) tablets are indicated for:

- The symptomatic relief of menopausal symptoms.
- ESTRACE may also contribute to the prevention of osteoporosis in naturally occurring or surgically induced estrogen-deficiency states when combined with other important therapeutics such as diet, calcium and vitamin D intake, smoking cessation and regular physical weight bearing exercises.

The use of ESTRACE in the prevention of osteoporosis is to be considered in light of other available therapies.

In patients with an intact uterus, ESTRACE should always be supplemented by sequential administration of a progestogen in order to prevent endometrial hyperplasia or carcinoma.

CONTRAINDICATIONS

Estrogen including ESTRACE should not be administered to patients with any of the following conditions:

- 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.
- Lactation
- Active or past history of arterial thromboembolic disease (e.g., stroke, myocardial infarction, coronary heart disease).
- Classical migraine
- 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 or diplopia, from ophthalmic vascular disease.
- Hypersensitivity 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.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial examined the health benefits and risks of combined *estrogen plus progestin* therapy (n=16,608) and *estrogen-alone* therapy (n=10,739) in postmenopausal women aged 50 to 79 years.^{5,40,41}

The *estrogen plus progestin* arm of the WHI trial indicated 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, 0.625mg/day) and medroxyprogesterone acetate (MPA, 2.5mg/day) for 5.2 years compared to those receiving placebo.⁴¹

The *estrogen-alone* arm of the WHI trial indicated an increased risk of *stroke* and *deep vein thrombosis* in hysterectomized women treated with CEE-alone (0.625mg/day) for 6.8 years compared to those receiving placebo.⁴⁰

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

1. Estrogens with or without progestins should not be prescribed for primary or secondary prevention of cardiovascular diseases.
2. Estrogens with or without progestins should be prescribed at the lowest effective dose for the approved indication.
3. Estrogens with or without progestins should be prescribed for the shortest period possible for the approved indication.
4. The use of ESTRACE for the prevention 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 hormone replacement therapy (HRT) versus 30 on placebo].⁴¹

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], 1.7cm [1.1] vs 1.5cm [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.⁵

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.⁴⁰

In a pivotal clinical study with ESTRACE (n=64) on the prevention of early post-menopausal bone loss (see **Clinical Trials**), three (3) abnormal mammograms were reported post-treatment, however, none showed evidence of malignancy.

It is recommended that estrogens not be given to women with existing breast cancer or those with a previous history of the disease. 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 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 counseling.

Endometrial hyperplasia & endometrial carcinoma

The use of unopposed estrogen by women with intact uteri increases the risk of endometrial hyperplasia and endometrial carcinoma. Estrogen should be prescribed with an appropriate dosage of a progestin in women with intact uteri in order to prevent endometrial hyperplasia/carcinoma.

During the conduct of a pivotal clinical study in an open-labeled study of 369 women (mean age = 49) with endogenous estrogen deficiency associated with menopausal symptoms (see **Clinical Trials**), endometrial biopsies were conducted in a subset of 32 subjects prior to and after therapy. Prior to therapy eleven (11) samples were considered abnormal: cystic hyperplasia (4), adenomatous hyperplasia (6) and mixed-inactive hyperplasia (1). One (1) sample biopsy remained abnormal after 11 months of treatment with ESTRACE, changing from cystic hyperplasia to benign cystic hyperplasia.

In a second pivotal clinical study on the prevention of early post-menopausal bone loss (see **Clinical Trials**), exit endometrial biopsy specimens were obtained for 21 subjects. Abnormalities consistent with estrogen stimulation of the endometrium were found in 27% of these subjects. Two (2) subjects had progression to the point of adenomatous hyperplasia and one (1) subject had atypical nuclear changes. No subjects, however, developed adenocarcinoma of the endometrium.

Ovarian cancer

Recent epidemiologic studies have found 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 WHI trial indicate that the use of *estrogen plus progestin* is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women.^{13, 19, 41} 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.^{40,41}

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).⁴¹

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.⁴⁰

HERS and HERS II findings

In the HERS study of postmenopausal women with documented heart disease (n=2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of CHD, treatment with 0.625mg/day oral conjugated equine estrogen (CEE) plus 2.5mg 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.¹⁹

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.¹³

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.

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 Interactions, Drug-Laboratory Test Interactions**).

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 VTE, including 8 more cases of pulmonary embolism.⁴¹

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.⁴⁰

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 $>30\text{kg/m}^2$) 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.

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**.

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 and free of dementia at baseline.^{34,35}

In the *estrogen plus progestin* arm of the WHIMS (n=4532), women with intact uteri were treated with daily 0.625mg conjugated equine estrogens (CEE) plus 2.5mg 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).³⁴

In the *estrogen-alone* arm of the WHIMS (n=2947), women with prior hysterectomy were treated with daily 0.625mg 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.³⁵

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).³⁵

Epilepsy

Particular caution is indicated in women with epilepsy, as HRT may cause an exacerbation of this condition.

Renal

Fluid retention

Estrogens may cause fluid retention. Therefore, particular caution is indicated in cardiac or renal dysfunction, epilepsy 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

Geriatrics (>65 years of age): The use of combined *estrogen plus progestin* in women aged 65 and over may increase the risk of developing probable dementia (see **Warnings and Precautions, Neurologic**).

Monitoring and Laboratory Tests

Before ESTRACE is administered, the patient should have a complete physical examination including a 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 Precaution, Hematologic and Drug Interactions, Drug-Laboratory Test Interactions**).

Cardiac disorders

Increase in blood pressure (see **Warnings and Precautions, Cardiovascular**); coronary thrombosis; palpitations.

Congenital, Familial and Genetic disorders

Precipitation or aggravation of porphyria cutanea tarda in predisposed individuals.

Endocrine disorders

Increased blood sugar levels; decreased glucose tolerance.

Eye disorders

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

Gastrointestinal disorders

Abdominal discomfort (cramps, pressure, pain, bloating); nausea; vomiting.

General disorders and administration site conditions

Anorexia; changes in appetite; changes in body weight; fatigue; change in libido.

Hepatobiliary disorders

Asymptomatic impaired liver function; cholestatic jaundice; gallbladder disorder.

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; dizziness; headaches; neuritis.

Psychiatric disorders

Irritability; mental depression; nervousness.

Renal and urinary disorders

Cystitis; dysuria; edema; sodium retention.

Reproductive system and breast disorders

Breakthrough bleeding; breast swelling, tenderness and secretion; changes in cervical erosion and amount of cervical secretion; change in menstrual flow; dysmenorrhea; dyspareunia; endometrial hyperplasia; increased cervical mucous; increase in size of uterine leiomyomata; pre-menstrual-like syndrome; reactivation of endometriosis; spotting; vaginal candidiasis; vaginal itching/discharge.

Skin and subcutaneous tissue disorders

Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; hirsutism and acne; itching, allergic reactions and rashes; loss of scalp hair; pigmentation of skin

Vascular disorders

Isolated cases of thromboembolic disorders; thrombophlebitis

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.

The following table summarizes the adverse events reported in a controlled, randomized, double-blind study with ESTRACE for the treatment of osteoporosis in 64 post-menopausal women. ESTRACE was administered in a cyclic manner for up to 18 months with an option to continue for an additional 6 months.

Table 1 Reported Adverse Events for More Than One Patient Per Dose Group: Symptoms by Treatment Assignment				
	0.5mg ESTRACE n=15 (%)	1.0mg ESTRACE n=16 (%)	2.0mg ESTRACE n=16 (%)	Placebo n=16 (%)
Gastrointestinal Disorders				
constipation	2 (13%)	1 (6%)	0	1 (6%)
nausea	0	0	0	2 (13%)
General Disorders & Administration Site Conditions				
asthenia	0	0	2 (13%)	1 (6%)
Investigations				
weight increased	3 (20%)	3 (19%)	2 (13%)	1 (6%)
Nervous System Disorders				
headache	0	0	1 (6%)	2 (13%)
Psychiatric Disorders				
nervousness	1 (7%)	2 (13%)	5 (31%)	2 (13%)
depression	2 (13%)	0	3 (19%)	3 (19%)
insomnia	0	1 (6%)	2 (13%)	2 (13%)
libido decreased	0	0	0	2 (13%)
Renal & Urinary Disorders				
edema	2 (13%)	1 (6%)	2 (13%)	1 (6%)
Reproductive System & Breast disorders				
menopausal systems ¹	10 (67%)	11 (69%)	11 (69%)	13 (81%)
vaginal hemorrhage	2 (13%)*	7 (44%)*	9 (56%)*	1 (6%)
vaginitis	1 (7%)	2 (13%)	0	0
uterine spasm	0	0	2 (13%)	0

* statistically significant at 5% level (Fisher's exact test)

¹ according to MedDRA dictionary, including symptoms such as vasomotor symptoms or hot flushes and vaginal dryness.

If adverse symptoms persist, the prescription of HRT should be reconsidered.

DRUG INTERACTIONS

Overview

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

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP 3A4).⁴³⁻⁴⁴ Therefore, inducers or inhibitors of CYP 3A4 may affect estrogen drug metabolism. Inducers of CYP 3A4 such as St. John's Wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in uterine bleeding profile. Inhibitors of CYP 3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Other preparations inducing liver enzymes, (e.g., barbiturates, hydantoin, meprobamate or phenylbutazone) may interfere with the activity of orally administered estrogens.

One in vitro study has shown cytochrome P450 1A2 (CYP 1A2) to be partially involved in the metabolism of 17 β -estradiol through hydroxylation.⁴³⁻⁴⁵ The clinical significance of CYP 1A2 metabolism is unknown.

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

Drug-Drug Interactions

Possible drug-drug interactions with ESTRACE specifically have not been established.

Drug-Food Interactions

Inhibitors of CYP 3A4 such as grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.⁴⁷⁻⁴⁸

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 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;
- Decreased antithrombin III (although following administration of ESTRACE for 28 days no effect on antithrombin III levels was seen); increased norepinephrine-induced platelet aggregability;
- Increased thyroxine-binding globulin (TBG) (although TBG was not affected in clinical trials with ESTRACE), leading to increased circulating total thyroid hormone (T₄) as measured by column or radioimmunoassay; T₃ resin uptake is decreased, reflecting the elevated TBG, free T₄ 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;
- Reduced serum folate concentration;
- Increased serum triglyceride and phospholipid concentrations;
- Impaired glucose tolerance.

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 HRT when relevant specimens are submitted.

Drug-Lifestyle Interactions

The effect of lifestyle choices (e.g., smoking) on the use of ESTRACE has not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The lowest dose of estrogen required to prevent menopausal symptoms and to prevent development of osteoporosis should be used. ESTRACE should be taken at the same time each day.

Recommended Dose and Dosage Adjustment

In general, estrogen is usually administered cyclically for the first 21 to 25 days of each month. In patients with intact uteri, a progestin should be sequentially administered for the last 12 to 14 days of estrogen administration in order to prevent development of endometrial hyperplasia/carcinoma as a result of estrogen stimulation.

In hysterectomized patients, estrogen alone should be given continuously.

Menopausal symptoms: Treatment of menopausal symptoms is usually initiated with 1mg ESTRACE tablet per day. Thereafter, the dosage should be adjusted to the needs of the individual. Attempts to taper or discontinue the medication should be made at 3 to 6 month intervals.

For prevention of osteoporosis: Prophylactic therapy with ESTRACE to prevent postmenopausal bone loss should be initiated with 0.5mg ESTRACE tablet per day as soon as possible after menopause. The dose may be titrated upward and downward based on the patient's clinical status and plasma estradiol levels. Ideally, plasma estradiol levels should be maintained around 50pg/mL.

Missed Dose

ESTRACE should be taken as soon as possible after missing a dose. However the missed dose should be skipped if it is almost time to take the next dose. Patients should be advised not to double the dose.

OVERDOSAGE

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

Treatment

Remove ingested drug by gastric lavage and give symptomatic treatment.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Estradiol is the most potent physiologic estrogen and, in fact, is the major estrogenic hormone secreted in humans. Estradiol controls the development and maintenance of the female sex organs, the secondary sex characteristics and the mammary glands as well as certain functions of the human uterus and accessory organs, particularly the proliferation of the endometrium, the development of the decidua, and the cyclic changes in the cervix and vagina. The production of estradiol by the ovaries is under the control of pituitary gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH). In menopausal women, the depletion of ovarian follicles leads to lower plasma estradiol and elevated plasma FSH and LH.

Pharmacodynamics

The active ingredient in ESTRACE tablets is derived from soy beans and it contains only one estrogen, 17 β -estradiol, which is structurally identical to the estradiol produced by the human ovary. Estrogens are secreted mainly by the gonads and in a very small amount by the adrenals. In addition, they are formed, to an important degree, from peripheral conversion of adrenal and gonadal androgens to estrogens.

Estradiol is the most potent of the known naturally occurring estrogens in stimulating the growth of the reproductive tissues. Estradiol promotes uterine growth in the rat without undergoing chemical transformation and responsive tissues, such as the uterus and vagina, show a characteristic affinity for estradiol.

Estrogen deficiency is manifested by hot flushes, sweating, insomnia, paresthesia, irritability, and urogenital atrophy. As replacement therapy in estrogen deficiency states (such as menopause), low doses of estradiol in cyclic regimens have been found to relieve such deficiency.

Estrogen deficiency is the main cause of postmenopausal bone loss and contributes to age-associated losses leading to osteoporosis. Numerous clinical studies have demonstrated that estrogen therapy prevents bone loss and reduces the incidence of vertebral, hip, and Colles' fractures.

Although the mechanism of action of estrogen on bone metabolism is still not completely elucidated, estrogens have been shown to have several effects: increase in renal tubular absorption of calcium, thus reducing urinary calcium; decrease in the sensitivity of bone to the parathyroid hormone (PTH); increase in the intestinal absorption of calcium and increase in circulating levels of active 1-25-dihydroxyvitamin D. Recent research has shown that osteoblasts also possess receptors for estrogens.

Pharmacokinetics

A number of steroids with 3 oxygen functions have been identified such as 16-epiestriol, 16-ketoestradiol, 16-hydroxyestrone and 2-methoxyestrone with estradiol being a precursor to these compounds.

Absorption: Micronized 17 β -estradiol is efficiently absorbed by the gastrointestinal tract.⁴⁹ The drug passes through the gastrointestinal mucosa and directly into the liver via the portal circulation before its access by the systemic circulation.⁵⁰

Distribution: Estrogens circulate in both unconjugated and conjugated forms in the blood, with the unconjugated estrogens, either free or bound to proteins, mainly albumin, or to the specific sex-hormone binding globulin (SHBG) which shows a great affinity for estradiol.

Metabolism: Estrogens are metabolized mainly in the liver, with the metabolites being conjugated with glucuronic acid or sulfuric acid and even double conjugates such as estriol-3-sulfate-16 α -glucuronide are formed. About 1/3 to 1/2 of the circulating estrogens are secreted in the bile and of this fraction 20% is reabsorbed after hydrolysis in the intestinal tract. The exact site of the hydrolysis is not known, but it probably takes place in the intestinal lumen and is catalyzed by enzymes secreted into the intestinal tract or present in the microflora.

Excretion: When administered to humans, about 65% of the dose is excreted in the urine, almost entirely in the water-soluble form as β -glucuronides or sulfate esters. Estrone, estradiol and estriol account for about 1/2 of the excreted products.

STORAGE AND STABILITY

Store at room temperature (15°-30°C). Keep container tightly closed and protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ESTRACE tablets are taken orally.

ESTRACE 0.5mg: Each tablet contains 0.5mg of micronized 17 β -estradiol. Nonmedicinal ingredients: acacia, cornstarch, dibasic calcium phosphate, lactose, magnesium stearate, silicon dioxide, talc. Tablet is white with MJ logo and “021” on one side and scored on the reverse.

ESTRACE 1mg: Each tablet contains 1mg of micronized 17 β -estradiol. Nonmedicinal ingredients: acacia, cornstarch, dibasic calcium phosphate, lactose, magnesium stearate, silicon dioxide, talc and colour dyes [FD&C Blue #1 aluminum lake and D&C Red #27 aluminum lake]. Tablet is lavender with MJ logo and “755” on one side and scored on the reverse.

ESTRACE 2mg: Each tablet contains 2mg of micronized 17β -estradiol. Nonmedicinal ingredients: acacia, cornstarch, dibasic calcium phosphate, lactose, magnesium stearate, silicon dioxide, talc and colour dyes [FD&C Blue #1 aluminum lake and FD&C Yellow #5 aluminum lake (tartrazine)]. Tablet is turquoise with MJ logo and “756” on one side and scored on the reverse.

ESTRACE tablets are available as round, flat-faced, bevel-edged compressed tablets containing 17β -estradiol in bottles of 100.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

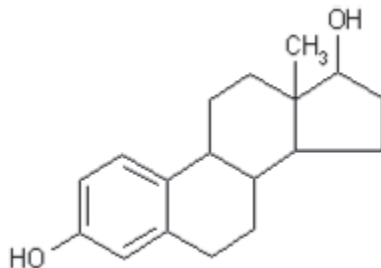
Drug Substance

Proper name: 17 β -estradiol

Chemical name: Estra-1,3,5(10)-triene-3,17 β -diol

Molecular formula and molecular mass: C₁₈H₂₄O₂ 272.39

Structural formula:



Physicochemical properties:

Estradiol is a white odorless crystalline solid, with a melting range of 173°-179°C. It is practically insoluble in water, freely soluble in alcohol, soluble in acetone, dioxane, chloroform, in solutions of fixed alkali hydroxides and sparingly soluble in vegetable oils.

CLINICAL TRIALS

Efficacy and Safety Studies

Study demographics and trial design

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age	Gender
139	Open-label	1mg/day ^{1,*} or 2mg/day ^{2,*} , orally (21 of 28 day cyclic regimen). Titration up to 4mg/day. Duration up to a year.	369	49 years	Female
7092	Randomized, double-blind, placebo-controlled, parallel group	Placebo, 0.5mg, 1mg or 2mg/day. 18 months with an option of continuing another 6 months.	64	52.8 years (Range: 42-58)	Female

1. Subjects with up to 5 hot flashes per day.

2. Subjects with more than 5 hot flashes per day.

* Dose titrated to a maximum of 4 mg/day for those not relieved by initial doses.

The safety and efficacy of ESTRACE in alleviating menopausal symptoms was evaluated in an open-label study (#139) of 369 women with endogenous estrogen deficiency associated with menopausal symptoms (Table 2).

The safety and efficacy of ESTRACE in preventing early post-menopausal bone loss was evaluated in a randomized, double-blind, placebo-controlled, parallel group, dose-ranging clinical study (#7092). Sixty-four (64) subjects with natural or surgical menopause were randomly assigned to one of 4 treatment groups: placebo (17), ESTRACE 0.5mg (15), 1mg (16) or 2mg (16) (Table 2). Treatment was administered as a 23 of 28 day cyclic regimen for a period of up to 18 months with an option to continue for an additional 6 months. All groups were supplemented with calcium tablets up to a total of 1500mg elemental calcium daily.

Study results

Symptomatic relief of menopausal symptoms

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
Relief from hot flashes	At doses of 1 to 4mg/day, ESTRACE provided relief of hot flashes in 95.6% of the subjects	Not applicable because there was no placebo or active control group.

In study #139, one hundred (100) subjects (27.1%) were on treatment from 0-4 months while 269 (72.9%) were treated for more than 4 months and up to more than one year for 48 patients (13.0%). Fifty-five (55) subjects dropped out of the study due to persistent menopausal symptoms (14), side effects (7), bleeding problem (1) or other reasons not related to treatment (33).

Overall, ESTRACE provided relief of hot flashes for 305 (95.6%) subjects (Table 3). Of the 319 subjects evaluated for efficacy, 77.4% were relieved of their symptoms with the initial dosage of 1 or 2mg, and 22.6% required a change to the initial dosage. In total, 8.1% of the subjects required dose increases up to 3 or 4mg. Other menopausal symptoms such as sweating, tingling, and genital atrophy were reported by 54%, 22% and 17% of the subjects, respectively. At the end of the study, only 11% of all patients reported having any of these symptoms.

The most commonly reported side effects during the course of the study were edema (29%), breast soreness (22%), uterine bleeding (7%) and weight gain (4%). Patients also complained of menopausal symptoms such as depression (36%), headache (19%), insomnia (18%), fatigue (13%) and decreased libido (6%).

In conclusion, ESTRACE at doses of 1 to 4mg/day given in a 21 of 28 day cyclic regimen was safe and efficacious for the treatment of symptoms related to endogenous estrogen deficiency.

Prevention of osteoporosis

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
Measurement of bone mineral density (n=45)	Non statistically significant trend found for increase in mean adjusted annual bone density at 0.5mg, 1mg or 2mg (0.2%, 1.9% and 1.0% respectively)	5.7% mean adjusted annual bone loss in Placebo group (p<0.01)

In study #7092, out of 64 enrolled patients, 23 did not complete the study and 1 did not participate from the onset. The only significant reason for failure to complete the study was treatment failure, which was highest in the placebo group at 31% (5/16). Seven (7) patients withdrew from the study due to adverse events. One (1) patient was taken off study medication due to concomitant illness. She developed edema and later was diagnosed with pelvic and costal metastatic disease and died. However, its relationship to therapy is unknown.

Efficacy was assessed in 45 subjects by measuring the spinal trabecular bone as determined by spinal quantitative computed tomography (SQCT) at baseline and at different time-points during the course of the trial. All doses of ESTRACE were equally effective at 12 months of treatment in preventing bone loss. In the placebo group, a significant mean adjusted annual bone loss of 5.7% (p<0.01) was observed, while in the ESTRACE (0.5mg, 1mg, 2mg) treated groups, there was trend for increase (0.2%, 1.9% and 1.0%, respectively) in the mean annual adjusted bone density which was not statistically significant (Table 4).

Safety was assessed in all patients by evaluating data from physical examinations, vital signs, hematological parameters, thyroid function and cholesterol metabolism before and after treatment. To address any estrogen-related risk factors, mammograms and endometrial biopsies were performed pre- and post-treatment. Vaginal bleeding as well as menopausal and vasomotor symptoms were assessed separately.

One serious adverse event occurred in this study. A subject in the 2mg ESTRACE group developed metastatic adenocarcinoma, and subsequently died. The relationship to study medication could not be determined as the origin of the cancer was unclear. The largest proportion of adverse events was related to the urogenital system, where 79% of subjects in the 4 groups experienced at least one event (see Table 1 in **Adverse Reactions**). The most frequently reported events were menopausal symptoms and vaginal bleeding. Vaginal bleeding was significantly more frequent (p<0.01) in the treatment groups compared to placebo and was dose-dependent. A statistically significant increase in weight was also reported for the 0.5mg and 1mg treatment groups. Vasomotor symptoms improved with ESTRACE treatment in a dose-dependent manner.

There were no clinically significant blood pressure changes in normotensive patients and no significant deterioration in the blood pressure of hypertensive subjects enrolled.

In conclusion, orally administered estradiol (ESTRACE) for the prevention of osteoporosis at doses of 0.5 to 2mg is safe and has a sparing effect on the axial skeleton, as determined by lumbar SQCT when administered in the early postmenopausal period.

DETAILED PHARMACOLOGY

Refer to the **Action and Clinical Pharmacology** section.

TOXICOLOGY

The role of estrogens in the development of endometrial carcinoma has been thoroughly investigated. Estrogens are capable of inducing cancer in laboratory animals, in which it rarely occurs spontaneously. In women, an increased incidence of endometrial carcinoma has been noted in hyperestrogenic states, such as estrogen-producing ovarian tumours. On chronic estrogenic administration, all intermediate stages between endometrial hyperplasia and true malignancy have been claimed. However, endometrial carcinoma has also been found in the absence of estrogenic stimulation.

The relationship between elevated plasma lipid levels and estrogen therapy is well documented. The mechanism of the rise in triglyceride levels is unclear; however, studies performed indicate that the triglyceride levels increase modestly and the cholesterol levels may or may not rise depending in part on the pre-existing levels.²⁶ These changes are associated with elevations of pre- β very low-density lipoproteins and occasionally β -low-density lipoproteins, without chylomicronemia.

A second and related effect of estrogenic drugs in the exacerbation of familial hyperlipoproteinemia is their diabetogenic action. Increasing hyperglycemia and hyperglyceridemia often occur together. Perfusion of the liver by the elevated concentrations of plasma glucose may induce an increased release of endogenous triglyceride. Exacerbation of pre-existing hyperglycemia or induction of hyperglycemia by estrogens was uniform in the four patients in a previous study.¹² Carbohydrate tolerance improved when estrogens were discontinued.

Although plasma insulin levels are apparently increased on estrogen therapy, the presence of increased growth hormone levels raises the question of increased peripheral insulin resistance and a theoretical possibility of decreased tissue insulin. Tissue lipoprotein lipase requires adequate insulin levels to ensure normal function. The complex effects of estrogen on carbohydrate and insulin metabolism could then also affect tissue lipoprotein lipase and could further diminish clearance of triglycerides.

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

REFERENCES

1. Adlercreutz H. Hepatic metabolism of estrogens in health and disease. *N Engl J Med* 1974 May 9;290(19):1081-3.
2. Boston Collaborative Drug Surveillance Program. Surgically confirmed gallbladder disease, venous thromboembolism and breast tumors in relation to post-menopausal estrogen therapy. *N Engl J Med* 1974 Jan 3;290(1):15-9.
3. Callantine MR, Martin PL, Bolding OT, Warner PO, Greaney MO Jr. Micronized 17 β -estradiol for oral estrogen therapy in menopausal women. *Obstet Gynecol* 1975 July;46(1):37-41.
4. Campbell S, Whitehead M. Oestrogen therapy and the menopausal syndrome. *Clin Obstet Gynaecol* 1977 Apr;4(1):31-47.
5. Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* 2003 Jun 25;289(24):3243-53.
6. Christiansen C, Riis B. 17 β -Estradiol and continuous norethisterone: A unique treatment for established osteoporosis in elderly women. *J Clin Endocrinol Metab* 1990 Oct;71(4):836-41.
7. Christiansen C, Riis B. Five years with continuous combined oestrogen/progestogen therapy. Effects on calcium metabolism, lipoproteins and bleeding pattern. *Br J Obstet Gynaecol* 1990 Dec;97(12):1087-92.
8. Davis ME, Wiener M, Jacobson HI, Jensen EV. Estradiol metabolism in pregnant and nonpregnant women. *Am J Obstet Gynecol* 1963 Dec 15;87:979-90.
9. Eriksen EF, Colvard DS, Berg NJ, Graham ML, Mann KG, Spelsberg TC, et al. Evidence of estrogen receptors in normal human osteoblast-like cells. *Science* 1988 Jul 1;241(4861):84-6.
10. Ettinger B. Prevention of Osteoporosis: Treatment of estradiol deficiency. *Obstet Gynecol* 1988 Nov;72(5 Suppl):12S-17S.
11. Gal I, Kirman B, Stern J. Hormone pregnancy tests and congenital malformation. *Nature* 1967 Oct 7;216(5110):83.
12. Glueck CJ, Scheel D, Fishback J, Steiner P. Estrogen-Induced Pancreatitis in patients with previously covert Familial Type V Hyperlipoproteinemia. *Metabolism* 1972 Jul;21(7):657-66.

13. Grady S, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M et al for the HERS Research Group. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and estrogen/progestin replacement study follow-up (HERS II). *JAMA* 2002 Jul 3;288(1):49-57.
14. Greenblatt RB, Emperaire JC. Changing concepts in the management of the menopause. *Med Times* 1970 Jun;98(6):153-64.
15. Hammond CB, Maxson WS. Current Sstatus of estrogen therapy for the menopause. *Fertil Steril* 1982 Jan;37(1):5-25.
16. Hammond CB, Maxson WS. Estrogen replacement therapy. *Clin Obstet Gynecol* 1986 Jun;29(2):407-30.
17. Hedlund LR, Gallagher JC. The effect of age and menopause on bone mineral density of the proximal femur. *J Bone Miner Res* 1989 Aug;4(4):639-42.
18. Hoover R, Gray LA Sr, Cole P, MacMahon B. Menopausal estrogens and breast cancer. *N Engl J Med* 1976 Aug 19;295(8):401-5.
19. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group 1998 Aug 19;280(7):605-13.
20. Janerich DT, Piper JM, Glebatis DM. Oral contraceptives and congenital limb-reduction defects. *N Engl J Med* 1974 Oct 3;291(14):697-700.
21. Kletzky OA, Borenstein RB. Vasomotor instability of the menopause. In: Mishell DR, editor. *Menopause: physiology and pharmacology*. Chicago: Mosby-Year Book; 1987. p. 53-65.
22. Levy EP, Cohen A, Fraser FC. Hormone treatment during pregnancy and congenital heart defects. *Lancet* 1973 Mar 17;1(7803):611.
23. Lindsay R, Hart DM, Forrest C, Baird C. Prevention of spinal osteoporosis in oophorectomised women. *Lancet* 1980 Nov 29;2(8205):1151-4.
24. Lobo R. Prevention of postmenopausal osteoporosis. In: Mishell DR, editor. *Menopause: Physiology and pharmacology*. Chicago: Mosby-Year Book; 1987. p. 165-186.

25. Mack TM, Pike MC, Henderson BE, Pfeiffer RI, Gerkins VR, Arthur M, et al. Estrogens and endometrial cancer in a retirement community. *N Engl J Med* 1976 Jun 3;294(23):1262-7.
26. Molitch ME, Oill P, Oddell WD. Massive hyperlipemia during estrogen therapy. *JAMA* 1974 Feb 4;227(5):522-5.
27. Natchigall LE, Nachtigall RH, Nachtigall RD, Beckman EM. Estrogen replacement therapy. I: A 10-year prospective study in the relationship to osteoporosis. *Obstet Gynecol* 1979 Mar;53(3):277-81.
28. Netelenbos JC, Siregar-Emck MT, Schot LP, van Ginkel FC, Lips P, Leeuwenkamp OR. Short term effects of Org OD 14 and 17 β -oestradiol on bone and lipid metabolism in early post-menopausal women. *Maturitas* 1991 Jun;13(2):137-49.
29. Nora J, Nora A. Birth defects and oral contraceptives. *Lancet* 1973 Apr 28;1(7809):941-2.
30. Pfeiffer RI, Van Den Noort S. Estrogen use and stroke risk in post-menopausal women. *Am J Epidemiol* 1976 May;103(5):445-56.
31. Quigley ME, Martin PL, Burnier AM, Brooks P. Estrogen therapy arrests bone loss in elderly women. *Am J Obstet Gynecol* 1987 Jun;156(6):1516-23.
32. Riis B, Johansen J, Christiansen C. Continuous oestrogen-progestogen treatment and bone metabolism in post-menopausal women. *Maturitas* 1988 May;10(1):51-8.
33. Schiff I, Regestein Q, Tulchinsky D, Ryan KJ. Effects of estrogens on sleep and psychological state of hypogonadal women. *JAMA* 1979 Nov 30;242(22):2405-4.
34. Shumaker SA, Legault, C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: A Randomized Controlled Trial. *JAMA* 2003 May 28;289(20):2651-62.
35. Shumaker SA, Legault, C, Kuller L, Rapp SR, Thal L, Lane DS, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004 Jun 23;291(24):2947-58.
36. Smith DC, Prentice R, Thompson, DJ, Herrmann WJ. Association of exogenous estrogen and endometrial carcinoma. *N Engl J Med* 1975 Dec 4;293(23):1164-7.

37. Speroff L, Glass RH, Kase NG. Clinical gynecologic endocrinology and infertility. 4th ed. Baltimore: Williams & Wilkins; 1989. p. 121-61.
38. Stampfer MJ, Colditz GA, Willett WC, Manson JE, Rosner B, Speizer FE, et al. Postmenopausal estrogen therapy and cardiovascular disease: Ten-Year Follow-Up From the Nurses' Health Study. *N Engl J Med* 1991 Sep 12;325(11):756-62.
39. Weiss NS, Ure CL, Ballard JH, Williams AR, Daling JR. Decreased risk of fractures of the hip and lower forearm with postmenopausal use of estrogens. *N Engl J Med* 1980 Nov 20;303(21):1195-8.
40. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative Randomized Controlled Trial. *JAMA* 2004 Apr 14;291(14):1701-12.
41. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002 Jul 17;288(3):321-33.
42. Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. *N Engl J Med* 1975 Dec 4;293(23):1167-70.
43. Badawi AF, Cavalieri EL, Rogan EG. Role of human cytochrome P450 1A1, 1A2, 1B1 and 3A4 in the 2-, 4-, and 16 alpha-hydroxylation of 17 beta-estradiol. *Metabolism* 2001 Sep;50(9):1001-3.
44. Yamazaki H, Shaw PM, Guengerich P, Shimada T. Roles of cytochromes P450 1A2 and 3A4 in the oxidation of estradiol and estrone in human liver microsomes. *Chem Res Toxicol* 1998 Jun;11(6):659-65.
45. Brøsen K. Drug interactions and the cytochrome P450 system. The role of cytochrome P450 1A2. *Clin Pharmacokinet* 1995;29(Suppl 1):20-5.
46. Lin JH, Lu AYH. Inhibition and induction of cytochrome P450 and the clinical implications. *Clin Pharmacokinet* 1998 Nov;35(5):361-90.
47. Schubert W, Cullberg G, Edgar B, Hedner T. Inhibition of 17 beta-estradiol metabolism by grapefruit juice in ovariectomized women. *Maturitas* 1994 Dec;20(2-3):155-63.
48. Schubert W, Eriksson U, Edgar B, Cullberg G, Hedner T. Flavonoids in grapefruit juice inhibit the in vitro hepatic metabolism of 17 beta-estradiol. *Eur J Drug Metab Pharmacokinet* 1995 Jul-Sep;20(3):219-24.

49. Callantine MR, Martin PL, Bolding OT, Warner PO, Greany MO. Micronized 17 β -estradiol for oral estrogen therapy in menopausal women. *Obstet Gynecol* 1975 Jul;46(1):37-41.
50. Lobo RA, Cassidenti DL. Pharmacokinetics of oral 17 β -estradiol. *J Reprod Med* 1992 Jan;37(1) :77-84.
51. Health Products and Food Branch. Guidance for industry: Product monographs of non-contraceptive estrogen/progestin-containing products, effective April 12, 2006. Available at: [http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/hrt-ths/pm mp noncontracept e.html](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/hrt-ths/pm_mp_noncontracept_e.html).
52. Rodriguez C, Patel AV, Calle EE, Jacob EJ, Thun MJ. Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. *JAMA* 2001 Mar 21;285(11):1460-5.
53. Lacey JV , Mink PJ, Lubin JH, Sherman ME, Troisi R, Hartge P, et al. Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA* 2002 Jul 17;288(3):334-41.
54. Anderson GL, Judd HL, Kaunitz AM, Barad DH, Beresford SA, Pettinger M, et al; Women's Health Initiative Investigators. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA* 2003 Oct 1;290(13):1739-48.
55. Lacey JV, Brinton LA, Leitzmann MF, Mouw T, Hollenbeck A, Schatzkin A, et al. Menopausal hormone therapy and ovarian cancer risk in the National Institutes of Health – AARP diet and health study cohort. *J Natl Cancer Inst* 2006 Oct 4;98 (19):1397-405.
56. Million Women Study Collaborators. Ovarian cancer and hormone therapy in the Million Women Study. *Lancet* 2007 May 19;369(9574):1703-10.

PART III: CONSUMER INFORMATION

 **ESTRACE®**
(17 β -estradiol Tablets)

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

ABOUT THIS MEDICATION**What the medication is used for:**

- Symptomatic relief of menopausal symptoms (hot flashes, dryness, itching and burning in and around the vagina)
- ESTRACE may also contribute to the prevention of osteoporosis, when combined with other important therapeutics such as diet, calcium and vitamin D intake, smoking cessation and regular physical weight bearing exercises. Osteoporosis is a thinning of the bones that makes them weaker and easier to break.

Use of ESTRACE is to be considered in light of other available therapies for the prevention of postmenopausal osteoporosis. 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 ESTRACE.

ESTRACE 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.

Important

If you still have your uterus (womb), talk to your doctor about adding a progestin (another female hormone) to ESTRACE to prevent cancer of the uterus.

What it does:

ESTRACE replaces diminishing estrogen production by the body.

Estrogens are female hormones that are produced by the body and are necessary for the normal sexual development and the regulation of menstrual periods during the childbearing years.

Low estrogen levels in menopause can also cause osteoporosis, which is a thinning of the bones that make them weaker and easier to break. Estrogens can help prevent osteoporosis related to menopause.

When it should not be used:

You should not take ESTRACE if you:

- Have liver disease
- Have (or have had) a personal history of known or suspected estrogen-dependent cancer such as cancer of the uterus (endometrial cancer)
- Have abnormal growth of the lining of the uterus (endometrial hyperplasia)
- Have (or have had) a personal history of known or suspected breast cancer
- Have unusual or undiagnosed genital bleeding
- may be pregnant or are nursing
- Have (or have had) a stroke or coronary heart disease (including heart attack and/or angina)
- have migraines
- Have (or have had) blood clot disorders, including blood clots in the legs or lungs or thrombophlebitis (blood clot and inflammation of the veins).
- Have partial or complete loss of vision due to blood vessel disease in the eye
- Are allergic to estradiol or any other ingredient in ESTRACE tablets (see **What the medicinal ingredient is and What the nonmedicinal ingredients are**)

What the medicinal ingredient is:

17 β -estradiol

What the nonmedicinal ingredients are:

Acacia, cornstarch, dibasic calcium phosphate, lactose, magnesium stearate, silicon dioxide, talc and colour dyes [FD&C Blue #1 aluminum lake and D&C Red #27 aluminum lake (1mg tablet), FD&C Blue #1 aluminum lake and FD&C Yellow #5 aluminum lake (tartrazine) (2mg tablet)].

What dosage forms it comes in:

The dosage form is a tablet. ESTRACE is provided in 0.5mg, 1mg and 2mg strength tablets.

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 *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 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 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 hormone replacement therapy (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 the 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.

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 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 ESTRACE 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 [tissue from the endometrium, found outside the uterus (generally in the pelvic cavity)].
- Have a history of liver disease, 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 or 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
- Recent or future surgery

- Control anxiety (e.g., meprobamate)
 - Treat bacterial infection such as antibiotics containing rifampicin (also called rifampin)
- Grapefruit juice and some herbal products (e.g. St. John’s Wort) available over-the-counter may also interact with ESTRACE.

Tell your doctor or pharmacist if you are taking any other medications, including prescription medications, over-the-counter medications, vitamins or herbal products.

PROPER USE OF THIS MEDICATION

Usual dose:

Your doctor will prescribe the lowest dose of estrogen needed to prevent menopausal symptoms or the development of osteoporosis. Estrogen is usually administered for the first 21 days to 25 days of each month. Take one tablet of ESTRACE at the same time each day.

- Treatment of menopausal symptoms: Initial treatment consists of a 1mg tablet per day. Every 3 to 6 months, you and your doctor should discuss whether you should reduce the dose of ESTRACE or stop taking ESTRACE.
- Prevention of osteoporosis: Initial treatment consists of a 0.5mg tablet per day as soon as possible after menopause.

If your uterus has been removed (hysterectomy), you will take ESTRACE every day of the month. If you have a uterus, you will take ESTRACE on certain days of the month as directed by your doctor. You will also take a progestin on certain days of the month to prevent abnormal growth of the lining of your uterus. Your doctor may adjust the dose according to your individual needs.

Overdose:

In women, overdosage of ESTRACE may cause nausea, breast discomfort, fluid retention, and vaginal bleeding.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take it as soon as possible. However, if it is almost time to take your next dose, skip the missed dose and go back to the regular dosing schedule. Do not double dose.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with ESTRACE include:

- Certain drugs used to:
 - Prevent blood clots
 - Control diabetes
 - Control high blood pressure
 - Prevent inflammation (containing phenylbutazone)
 - Control epilepsy (e.g., phenobarbital, phenytoin, or carbamazepine)

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Women rarely have severe side effects from taking estrogens. However if you have any of the symptoms listed below you must speak with your doctor immediately.

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	Abdominal pain, nausea or vomiting		√	
Uncommon	Lumps or discharge from the breast		√	√
	Crushing chest pain or chest heaviness			√
	Pain or swelling in the leg or feet			√
	Pain in groin		√	
	Persistent sad mood			√
	Sharp pain in the chest, coughing blood or sudden shortness of breath			√
	Sudden partial or complete loss of vision			√
	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg			√
	Sudden loss of coordination			√
	Unexpected vaginal bleeding		√	
	Yellowing of the skin (jaundice)			√

Side effects that usually do not need medical attention

These side effects go away during treatment as your body adjusts to the medicine. However, check with your doctor if they continue or become bothersome:

- Bloating
- Stomach cramps
- Headaches (mild)
- Dizziness (mild)

Also, many women who are taking estrogens with a progestin will start having monthly vaginal bleeding, similar to menstrual periods again. This effect will continue for as long as the medicine is taken. However, monthly bleeding should not occur in women who have had their uterus removed by surgery (hysterectomy).

Other possible side effects

- Breast pain and swelling
- Irregular vaginal bleeding or spotting
- Vaginal itching/discharge or pain
- Depression, nervousness, and/or irritability
- Allergic reaction and rash
- Hair loss or abnormal hair growth
- Increased blood sugar levels
- Change in blood pressure
- Acne
- Change in cholesterol and/or triglyceride levels
- Change in weight

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

HOW TO STORE IT

Store the bottle at room temperature (15°-30°C). Keep container tightly closed and protect from light. **Keep out of the 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 0701E
Ottawa, Ontario
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 the sponsor, Acerus Pharmaceuticals Corporation, at: 1 844 850 1642 or AcerusPV@innomar-strategies.com

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