

ESTRADIOL VALERATE INJECTION, USP Rx Only

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of different estrogens or different routes of administration alter the relative endometrial risk profile than synthetic estrogens at equivalent doses. (See **WARNINGS, Malignant Neoplasms, Endometrial cancer**.)

CARDIOVASCULAR AND OTHER RISKS

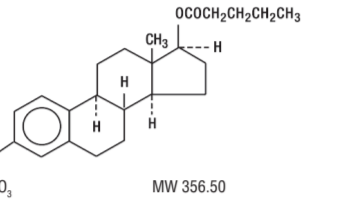
Estrogens and progestins should be used for the prevention of cardiovascular disease. (See **WARNINGS, Cardiovascular disorders**.) The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.) The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women (50 to 69 years of age) during 5 years of treatment with oral conjugated estrogens and MPA relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen alone therapy. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

Estradiol Valerate Injection, USP contains estradiol valerate, a long-acting estrogen in sterile oil solutions for intramuscular use. These solutions are clear, colorless to yellow. Formulations per mL: 20 mg estradiol valerate in a vehicle containing 224 mg benzyl alcohol, 20 mg benzyl alcohol, and castor oil; 40 mg estradiol valerate in a vehicle containing 447 mg benzyl benzoate, 20 mg benzyl alcohol, and castor oil. Estradiol valerate is designated chemically as $\text{estr-1,3,20(10)-trien-3,17-diol(17\beta)-17-pentanoate}$.

Graphical formula:



CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is biologically most active. Estrone and estradiol are the major estrogens in the circulation. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women. Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

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

Pharmacokinetics

Absorption

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

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

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estrone, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens. 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 estrogens species. This results in limited oral potency. By contrast, synthetic estrogens, such as ethinyl estradiol, are degraded very slowly in the liver and other tissues, which results in their high intrinsic potency. Estrogen drug products administered by non-oral routes are not subject to first-pass metabolism, but also undergo significant hepatic uptake, metabolism, and enterohepatic recirculation.

Excretion

Estrone, estrone, and estradiol are excreted in the urine along with glucuronide and sulfate conjugates.

Drug Interactions

In vivo and *in vitro* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect the metabolism of estradiol. St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of P-glycoprotein such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Clinical Studies

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of oral 0.625 mg conjugated estrogens (CE) per day alone or the use of oral 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse effect. The secondary endpoint was the incidence of stroke, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to cancer. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms. The CE/MPA substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specific benefits included in the "global index." Results of the CE/MPA substudy, which included 16,608 women (average age of 63 years, range 50 to 78, 85.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 1 below.

Event*	Relative Risk (95% CI)†		Absolute Risk per 10,000 Person-years	
	Relative Risk CE/MPA vs. placebo	Placebo n = 8102	CE/MPA n = 8506	
CHD events	1.29 (1.02-1.63)	30	37	
- Non-Fatal MI	1.22 (1.02-1.72)	23	30	
CHD death	1.18 (0.79-1.97)	6	6	
Invasive breast cancer*	1.26 (1.00-1.59)	21	28	
Stroke	1.41 (1.07-1.85)	21	29	
Pulmonary embolism	2.13 (1.39-3.25)	6	16	
Colorectal cancer*	0.83 (0.43-0.92)	16	10	
Endometrial cancer	0.68 (0.41-1.17)	6	5	
Hip fracture	0.66 (0.45-0.98)	15	10	
Death due to causes other than the events above	1.02 (0.74-1.14)	40	37	
Global Index*	1.15 (1.03-1.28)	151	170	
Deep vein thrombosis*	2.07 (1.49-2.87)	13	26	
Vertebral fractures*	0.66 (0.44-0.98)	15	9	
Other osteoporotic fractures*	0.77 (0.69-0.86)	170	131	

*Adapted from JAMA, 2002; 288:321-333

†Includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer

*A subset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes

†Not included in Global Index

*Nominal confidence intervals unadjusted for multiple looks and multiple comparisons

For those outcomes included in the "global index," the absolute excess risks per 10,000 women-years in the group treated with CE/MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNING, WARNINGS, and PRECAUTIONS**.)

Women's Health Initiative Memory Study

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 to 79 years of age) to evaluate the effects of CE/MPA (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate) on the incidence of probable dementia (primary outcome) compared with placebo. After an average follow-up of 4 years, 40 women in the estrogen/progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI: 1.21 to 3.45) compared to placebo. Differences between groups were apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNING, WARNINGS, and DEMENTIA**.)

INDICATIONS AND USAGE

Estradiol Valerate Injection is indicated in the:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. When prescribing solely for the treatment of symptoms of vasomotor symptoms, the lowest effective dose should be used.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
3. Treatment of hypoestrogenism due to hypopituitarism, castration or primary ovarian failure.
4. Treatment of advanced androgen-dependent carcinoma of the prostate (or primary ovarian failure).

CONTRAINDICATIONS

Estradiol Valerate Injection should not be used in women with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of cancer of the breast.
3. Known or suspected estrogen-dependent neoplasia.
4. Active deep vein thrombosis, pulmonary embolism or a history of these conditions.
5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6. Liver dysfunction or disease.
7. Known or suspected pregnancy. Estradiol Valerate Injection should not be used in patients with known hypersensitivity to its ingredients.
8. Known or suspected pregnancy. There is no indication for Estradiol Valerate Injection in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives including during early pregnancy. (See **PRECAUTIONS**.)

WARNINGS

See **BOXED WARNINGS**.

The use of unopposed estrogens in women who have a uterus is associated with an increased risk of endometrial cancer.

1. Cardiovascular disorders

Estrogen and estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history of family history of VTE, obesity, and systemic lupus erythematosus) are managed appropriately.

a. Coronary heart disease and stroke

In the Women's Health Initiative (WHI) study, an increase in the number of myocardial infarctions and strokes has been observed in women receiving CE compared to placebo. These observations are preliminary. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In the CE/MPA substudy of WHI, an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs. 30 per 10,000 women-years). The increase in risk was observed in year one and persisted.

In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs. 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n=2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study, HERS) treatment with CE/MPA (0.625mg/2.5mg per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with documented heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 to 6 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a retrospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. Venous thromboembolism (VTE)

In the Women's Health Initiative (WHI) study, an increase in VTE has been observed in women receiving CE compared to placebo. These observations are preliminary. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep vein thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the CE/MPA group compared to 16 per 10,000 women-years in the placebo group.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant neoplasms

a. Endometrial cancer

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for use for ten years or more. This risk has been shown to persist for at least 1 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent doses. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. Breast cancer

The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) substudy of CE/MPA (See **CLINICAL PHARMACOLOGY, Clinical Studies**). The relative risks are generally consistent with those of the WHI clinical trial and report to not significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration.

The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported increased risks of breast cancer in women taking estrogen alone therapy, and smaller increased risk for estrogen alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about five years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy.

In the CE/MPA substudy, 26% of the women reported prior use of estrogen alone and/or estrogen/progestin combination therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval [CI] 1.01 to 1.54) for the overall population. The overall absolute risk was 40 vs. 38 cases per 10,000 women-years for CE/MPA compared with placebo. In the same study, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

c. Ovarian cancer

The CE/MPA substudy of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% confidence interval 0.77 to 3.24) but was not statistically significant. The absolute excess risk was 0.95 (95% confidence interval 0.12 to 1.48), and similar for women with and without menopausal meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The primary analysis, using case-control comparisons, included 12,110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% confidence interval [CI] 1.32 to 1.50); there was no difference in the risk between women who used hormonal therapy for 2 years or less compared with 3 years or more than 5 years (median of 10 years) of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27 to 1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

3. Dementia

In the Women's Health Initiative Memory Study (WHIMS), 4,532 generally healthy postmenopausal women 65 years of age and older were studied, of whom 35% were 70 to 74 years of age and 18% were 75 or older. After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n = 2,229) and 21 women in the placebo group (0.9%, n = 2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% confidence interval 1.21 to 3.45), and similar for women with and without menopausal meta-analysis of 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% confidence interval [CI] 1.32 to 1.50); there was no difference in the risk between women who used hormonal therapy for 2 years or less compared with 3 years or more than 5 years (median of 10 years) of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27 to 1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

4. Gallbladder disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported. Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

5. Hypocalcemia

Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

6. Visual abnormalities

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

PRECAUTIONS

A. GENERAL

1. Addition of a progestin when a woman has not had a hysterectomy
Studies of the addition of a progestin to 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, are reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer.

2. Elevated blood pressure
In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

3. Hypertriptycidenemia

In patients with pre-existing hypertension, estrogen therapy may be associated with elevations of plasma triptolides leading to pancreatitis and other complications.

4. Impaired liver function and history of cholelithiasis/jaundice

Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholelithiasis/jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

5. Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. Fluid retention

Estrogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

PATIENT INFORMATION

ESTRADIOL VALERATE INJECTION, USP

Read this **PATIENT INFORMATION** before you start taking Estradiol Valerate Injection and read what you get each time you refill Estradiol Valerate Injection.

There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT ESTRADIOL VALERATE INJECTION (AN ESTROGEN HORMONE)?

Estrogens increase the chances of getting cancer of the uterus. Report any unusual vaginal bleeding right away while you are taking estrogens. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

Do not use estrogens with or without progestins to prevent heart disease, heart attacks, or strokes. Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. Using estrogens with progestins may increase your risk of dementia. You and your healthcare provider should talk regularly about whether you still need treatment with Estradiol Valerate Injection.

Coronary heart disease and stroke
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