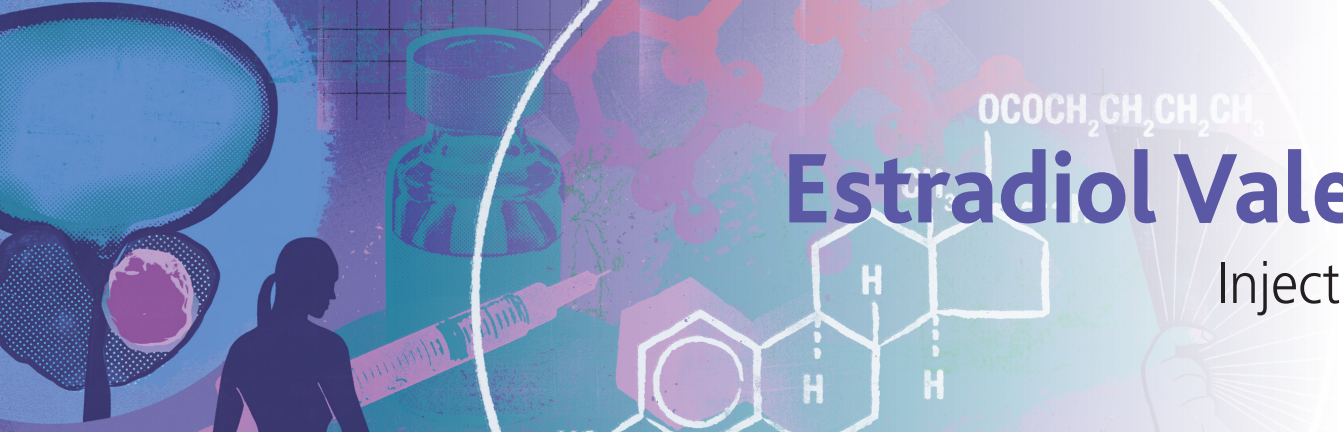

Estradiol Valerate

Injection, USP

FREQUENTLY ASKED QUESTIONS

1. **Is Estradiol Valerate Injection, USP a boxed warning product?**
   Yes

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 "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses.

CARDIOVASCULAR AND OTHER RISKS
Estrogens and progestins should not be used for the prevention of cardiovascular disease. 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.

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen alone therapy.

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.

For additional safety information, including BOXED WARNING, please see the Full Prescribing Information.

You are encouraged to report adverse drug events to American Regent Inc. at 1-800-734-9236, or to the FDA by visiting www.fda.gov/medwatch or by calling 1-800-FDA-1088.

2. **What are the ingredients in Estradiol Valerate Injection, USP?**
   Estradiol Valerate Injection, USP is supplied in 5 mL multiple-dose vials[1]:
   - 20 mg/mL vial contains estradiol valerate in a solution of benzyl benzoate, benzyl alcohol, and castor oil
   - 40 mg/mL vial contains estradiol valerate in a solution of benzyl benzoate, benzyl alcohol, and castor oil

3. **What is the preservative in Estradiol Valerate Injection, USP?**
   Both the 20 mg/mL vial and the 40 mg/mL vial contain 20 mg/mL of benzyl alcohol as a preservative.[1]

4. **How is estradiol valerate administered?**
   Estradiol Valerate Injection, USP contains estradiol valerate, a long-acting estrogen in sterile oil solutions for intramuscular injection.[1]

5. **How stable is the vial after puncture?**
   The extended stability of Estradiol Valerate Injection, USP after vial puncture has not been studied. Chapter 797 of *United States Pharmacopeia* recommends up to 28 days as the beyond-use date for opened or "entered" (ie, needle-punctured) multi-dose vials of sterile pharmaceutical injection containing antimicrobial preservatives.[2]

6. **How should Estradiol Valerate Injection, USP be stored?**
   Store Estradiol Valerate Injection, USP at room temperature between 20°C to 25°C (68°F to 77°F). (See USP-Controlled Room Temperature.) PROTECT FROM LIGHT. Store vial in carton until used.[1]

7. **Is Estradiol Valerate Injection, USP latex-free?**
   The vial closure is not made with natural rubber latex.

Estradiol Valerate Injection, USP

For intramuscular use

INDICATIONS AND USAGE

Estradiol Valerate Injection is indicated in the:

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

IMPORTANT SAFETY INFORMATION

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CONTRAINDICATIONS

Estradiol Valerate Injection should not be used in women with any of the following conditions:
Undiagnosed abnormal genital bleeding. Known, suspected, or history of cancer of the breast. Known or suspected estrogen-dependent neoplasia. Active deep vein thrombosis, pulmonary embolism or a history of these conditions. Active or recent arterial thromboembolic disease. Liver dysfunction or disease. Estradiol Valerate Injection should not be used in patients with known hypersensitivity to its ingredients. Known or suspected pregnancy. There is no indication for Estradiol Valerate Injection in pregnancy.

WARNINGS

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

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. Should they occur or be suspected, estrogens should be discontinued immediately.

Coronary heart disease and stroke - An increase in the number of myocardial infarctions and strokes has been observed in women receiving CE which was observed in year one and persisted.

Large doses of estrogen have been shown in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

Venous thromboembolism (VTE) - An increase in VTE has been observed in women receiving CE. Deep venous thrombosis and pulmonary embolism was observed in women receiving CE/MPA, which was observed during the first year and persisted.

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.

Malignant neoplasms

Endometrial cancer - The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. Clinical surveillance of all women taking estrogen/progestin combinations is important.

Breast cancer - The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation.

Ovarian cancer - Estrogen plus progestin increased the risk of ovarian cancer. Women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer.

Dementia
There is an increased risk of probable dementia for CE/MPA.

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

Hypercalcemia
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.

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

PRECAUTIONS
GENERAL
Addition of a progestin when a woman has not had a hysterectomy - Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have 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.

Elevated blood pressure - Substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. Blood pressure should be monitored at regular intervals.

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

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

Hypothyroidism - Estrogen administration leads to increased thyroid-binding globulin levels. 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.

Fluid retention - Estrogens may cause fluid retention, therefore careful observation is warranted.

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

Exacerbation of endometriosis - Endometriosis may be exacerbated with administration of estrogens. Cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen alone therapy.

Exacerbation of other conditions - Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

Hypercoagulability - Women taking estrogen replacement therapy may have hypercoagulability.

Uterine bleeding and mastodynia - Patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.

Patient Information
Physicians are advised to discuss the PATIENT INFORMATION leaflet with patients for whom they prescribe Estradiol Valerate Injection.

Laboratory Tests
Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels.

Drug/Laboratory Test Interactions
Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased thyroid-binding globulin levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine, T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered.

Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin, sex hormone binding globulin), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma HDL and HDL2 cholesterol subfraction concentrations, reduced LDL cholesterol concentrations, increased triglycerides levels.

Impaired glucose tolerance.

Reduced response to metyrapone test.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer.

Pregnancy
Estradiol Valerate Injection should not be used during pregnancy.

Nursing Mothers
Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when Estradiol Valerate Injection is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established. Large and repeated doses of estrogen over an extended period of time may accelerate epiphyseal closure. Periodic monitoring of bone maturation and effects on epiphyseal centers is recommended in patients in whom bone growth is not complete.

Geriatric Use
Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification.

ADVERSE REACTIONS - See **BOXED WARNINGS, WARNINGS**, and **PRECAUTIONS**.
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following additional adverse reactions have been reported with estrogen and/or progestin therapy.

Genitourinary system - Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea, increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

Breasts - Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.

Cardiovascular - Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

Gastrointestinal - Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis, enlargement of hepatic hemangiomas.

Skin - Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.

Eyes - Retinal vascular thrombosis; intolerance to contact lenses.

Central Nervous System - Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy, dementia.

Miscellaneous - Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthralgias; leg cramps; changes in libido; urticaria, angioedema, anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides.

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REF-1504 12/2022

Estradiol Valerate

Injection, USP

Pack NDC#	Strength	Supplied as	Shelf pack
0517-0420-01	20 mg/mL	5 mL Multiple-dose vial	1
0517-0440-01	40 mg/mL	5 mL Multiple-dose vial	1

Pack NDC#	ABC/SAP	Cardinal	McKesson	Morris & Dickson
0517-0420-01	10236255	5649348	1546050	880427
0517-0440-01	10236312	5649348	1545904	880435

You are encouraged to report adverse drug events (ADEs) to American Regent©:
T 1.800.734.9236; **E** pv@americanregent.com; **F** 1.610.650.0170

ADEs may also be reported to the FDA:
1.800.FDA.1088 or www.fda.gov/medwatch

Medical information:
T 1.888.354.4855 (9:00 am – 5:00 pm Eastern Time, Monday – Friday)
www.americanregent.com/medical-affairs

For medical information outside of normal business hours
that cannot wait until the next business day, please call 1.877.845.6371

REFERENCES
1. Estradiol Valerate Injection, USP. Package insert. American Regent, Inc.
2. *The United States Pharmacopeia: The National Formulary*. United States Pharmacopeial Convention; 2020.

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