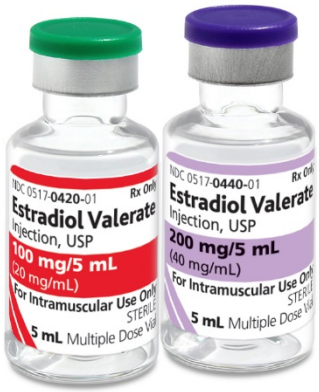
American Regent Introduces Estradiol Valerate Injection, USP; AO Rated and Therapeutically Equivalent to Delestrogen®[1, 2]



Estradiol Valerate Injection is supplied in a 5 mL glass vial in a strength of 100 mg/5 mL (20 mg/mL), and in a 5 mL glass vial in a strength of 200 mg/5 mL (40 mg/mL).

Shirley, NY – June 3, 2020: American Regent announces the introduction and availability of Estradiol Valerate Injection, USP – AO Rated and therapeutically equivalent to Delestrogen®[1,2]. Estradiol Valerate Injection is indicated in the:

- Treatment of moderate to severe vasomotor symptoms associated with the menopause.
- 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.
- Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
- Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).

"We are proud to add Estradiol Valerate Injection to our robust product line of products that are manufactured in America. We are also pleased to provide patients with another treatment option from American Regent," stated Harsher Singh, *Vice President, Chief Commercial and Strategic Officer at American Regent, Inc.*

This product is available for immediate shipment. Customers can order Estradiol Valerate Injection, USP through their wholesaler/distributor, or by contacting our Customer Support Group at 1-800-645-1706.

Estradiol Valerate Injection, USP is supplied as follows:

Pack NDC#	Strength	Supplied As	Shelf Pack
0517-0420-01	100 mg/5 mL (20 mg/mL)	5 mL Multiple Dose Vial	1
0517-0440-01	200 mg/5 mL (40 mg/mL)	5 mL Multiple Dose Vial	1

See the following Important Safety Information, including **BOXED WARNING**, in addition to the product's Full Prescribing Information.

For additional information, please visit www.americanregent.com.

References

1. Approved Drug Products with Therapeutic Equivalence Evaluations: https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=090920#27598 Accessed May 13, 2020.
2. Delestrogen® is a registered trademark of Par Sterile Products, LLC.

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A Daiichi Sankyo Group Company

PP-EV-US-0005 6/2020

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

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.

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.

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

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 - An 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 - Risks may be associated with the use of progestins with estrogens compared to estrogen-alone regimens, including a possible increased risk of breast cancer.

Elevated blood pressure - 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, VIll 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; arthalgias; leg cramps; changes in libido; urticaria, angioedema, anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides.

For additional safety information, including BOXED WARNING, please see 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.**

REF-1504 4/2020

You are encouraged to report Adverse Drug Events (ADEs) to American Regent:
Email: pv@americanregent.com; **Fax:** 1-610-650-0170;
Phone: 1-800-734-9236

ADEs may also be reported to the FDA:
1-800-FDA-1088 or to www.fda.gov/medwatch

Drug Information:
1-888-354-4855
(9:00 am – 5:00 pm Eastern Time, Monday – Friday)

For urgent drug information outside of normal business hours,
assistance is available at:
1-877-845-6371

About American Regent
American Regent, Inc., a Daiichi Sankyo Group company, is a top-10 injectable manufacturer. For over 50 years, American Regent has been developing, manufacturing and supplying quality generic and branded injectables for healthcare providers. For nearly 20 years, we have been a leader in IV iron therapy.

American Regent is committed to US-based manufacturing. In 2018, more than 99% of units supplied were manufactured in our US-based facilities, making us uniquely positioned to quickly mobilize and respond to shortages or changes in market needs.

Speed counts. Flexibility matters. Reliability and quality are paramount. Because patients should never have to wait for the medications they need.

For more information, please visit www.americanregent.com.

About Daiichi Sankyo Group
Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical therapies to improve standards of care and address diversified, unmet medical needs of people globally by leveraging our world-class science and technology. With more than 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 15,000 employees around the world draw upon a rich legacy of innovation and a robust pipeline of promising new medicines to help people. In addition to a strong portfolio of medicines for cardiovascular diseases, under the Group's 2025 Vision to become a "Global Pharma Innovator with Competitive Advantage in Oncology," Daiichi Sankyo is primarily focused on providing novel therapies in oncology, as well as other research areas centered around rare diseases and immune disorders.

For more information, please visit: www.daiichisankyo.com.

Daiichi Sankyo, Inc., headquartered in Basking Ridge, New Jersey, is a member of the Daiichi Sankyo Group.
For more information on Daiichi Sankyo, Inc., please visit: www.dsi.com.