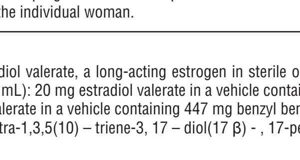
ESTRADIOL VALERATE
INJECTION, USP
Rx Only

> **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 "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses. (See **WARNINGS, Malignant neoplasms, *Endometrial cancer***.)
> **CARDIOVASCULAR AND OTHER RISKS**
> Estrogens and progestins should not 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 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. (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 benzoate, 20 mg benzyl alcohol (preservative), 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 estra-1,3,5(10) – triene-3, 17 – diol(17 β) - , 17-pentanoate.
Graphic formula:



$C_{23}H_{32}O_3$ MW 356.50

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 substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg 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.

Distribution
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 estriol, 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 estrogenic species. This results in limited oral potency. By contrast, synthetic estrogens, such as ethinyl estradiol and the nonsteroidal estrogens, are degraded very slowly in the liver and other tissues, which results in their high intrinsic potency. Estrogen drug products administered by non-oral routes are not subject to first-pass metabolism, but also undergo significant hepatic uptake, metabolism, and enterohepatic recycling.

Excretion
Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Drug Interactions
In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as 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 CYP3A4 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 outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. 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 specified 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 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 1 below:

Table 1. RELATIVE AND ABSOLUTE RISK SEEN IN THE CE/MPA SUBSTUDY OF WHI[a]

Event[c]	Relative Risk CE/MPA vs. placebo at 5.2 Years (95% CI*)	Placebo n = 8102	CE/MPA n = 8506
		Absolute Risk per 10,000 Person-years	
CHD events	1.29 (1.02-1.63)	30	37
Non-fatal MI	*1.32 (1.02-1.72)*	*23*	*30*
CHD death	*1.18 (0.70-1.97)*	*6*	*7*
Invasive breast cancer[b]	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global Index[c]	1.15 (1.03-1.28)	151	170
Deep vein thrombosis[d]	2.07 (1.49-2.87)	13	26
Vertebral fractures[d]	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures[d]	0.77 (0.69-0.86)	170	131

[a] adapted from JAMA, 2002; 288:321-333
[b] includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer
[c] 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
[d] 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 per 10,000 women-years 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 years of age and older) 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 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNING** and **WARNINGS, Dementia**.)

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).

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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. 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 inadvertently 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 or family history of VTE, obesity, and systemic lupus erythematosus) should be 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 established coronary 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 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective 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 venous 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. The increase in VTE risk 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.

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 five to ten years or more and this risk has been shown to persist for at least 8 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 of equivalent estrogen dose. 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 results from observational studies are generally consistent with those of the WHI clinical trial and report no 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 an increased risk for estrogen/progestin combination hormone therapy, and a 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 1.01 to 1.54), and the overall absolute risk was 41 vs. 33 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs. 25 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs. 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy, 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 risk for CE/MPA versus placebo was 4.2 versus 2.7 cases per 10,000 women-years.

A 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 estimates by duration of the exposure (less than 5 years [median of 3 years] vs. greater 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 3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies** and **PRECAUTIONS, Geriatric Use**.)

It is unknown whether these findings apply to estrogen alone therapy.

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.

5. 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.

6. 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

A. GENERAL

1. 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.

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

4. 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.

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
Because 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.

What is Estradiol Valerate Injection?
Estradiol Valerate Injection is a medicine that contains estrogen hormones.

What is Estradiol Valerate Injection used for?
Estradiol Valerate Injection is used after menopause to:
- **reduce moderate to severe hot flashes.** Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 to 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."
  When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feeling of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women, the symptoms are mild, and they will not need estrogens. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether you still need treatment with Estradiol Valerate Injection.
- **treat moderate to severe dryness, itching, and burning in and around the vagina.** You and your healthcare provider should talk regularly about whether you still need treatment with Estradiol Valerate Injection to control these problems. If you use Estradiol Valerate Injection only to treat your dryness, itching, and burning in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.

Who should not take Estradiol Valerate Injection?
Do not start taking Estradiol Valerate Injection if you:
- **have unusual vaginal bleeding.**
- **currently have or have had certain cancers.** Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or had cancer, talk with your healthcare provider about whether you should take Estradiol Valerate Injection.
- **had a stroke or heart attack in the past year.**
- **currently have or have had blood clots.**
- **currently have or have had liver problems.**
- **are allergic to Estradiol Valerate Injection or any of its ingredients.** See the end of this leaflet for a list of ingredients in Estradiol Valerate Injection.
- **think you may be pregnant.**

Tell your healthcare provider:
- **if you are breastfeeding.** The hormone in Estradiol Valerate Injection can pass into your milk.
- **about all of your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **about all the medicines you take.** This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Estradiol Valerate Injection works. Estradiol Valerate Injection may also affect how your other medicines work.
- **if you are going to have surgery or will be on bed rest.** You may need to stop taking estrogens.

How should I take Estradiol Valerate Injection?
Estradiol Valerate Injection should be injected deeply into the upper, outer quadrant of the gluteal muscle following the usual precautions for intramuscular administration. By virtue of the low viscosity of the vehicles, the various preparations of Estradiol Valerate Injection may be administered with a small gauge needle (i.e., 20 Gauge x 1 1/2 inches long). Since the 40 mg potency provides a high concentration in a small volume, particular care should be observed to administer the full dose.
Estradiol Valerate Injection should be visually inspected for particulate matter and color prior to administration; the solution is clear, colorless to yellow. Storage at low temperatures may result in the separation of some crystalline material which redissolves readily on warming.
Note: A dry needle and syringe should be used. Use of a wet needle or syringe may cause the solution to become cloudy; however, this does not affect the potency of the material.
1. Start at the lowest dose and talk to your healthcare provider about how well that dose is working for you.
2. Estrogens should be used at the lowest dose possible for your treatment only as long as needed. The lowest effective dose of Estradiol Valerate Injection has not been determined. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with Estradiol Valerate Injection.

How should I dispose of used syringes and needles?
1. Do not re-use needles or syringes.
2. Do not throw the needles and syringes in household waste. These should be discarded into an appropriate container (such as a sharps container) immediately after use. Refer to state or local laws and regulations for appropriate container requirements.
3. Make sure the container is tightly capped.
4. Strategically place the container so as to minimize handling and keep out of the reach of children.
5. Label the container indicating the presence of used needles/sharps.
6. For disposal of containers containing used needles and syringes refer to the state or local laws and regulations or as instructed by your healthcare provider or pharmacist.

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- 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.

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Who should not take Estradiol Valerate Injection?
Do not start taking Estradiol Valerate Injection if you:
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- **had a stroke or heart attack in the past year.**
- **currently have or have had blood clots.**
- **currently have or have had liver problems.**
- **are allergic to Estradiol Valerate Injection or any of its ingredients.** See the end of this leaflet for a list of ingredients in Estradiol Valerate Injection.
- **think you may be pregnant.**

Tell your healthcare provider:
- **if you are breastfeeding.** The hormone in Estradiol Valerate Injection can pass into your milk.
- **about all of your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **about all the medicines you take.** This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Estradiol Valerate Injection works. Estradiol Valerate Injection may also affect how your other medicines work.
- **if you are going to have surgery or will be on bed rest.** You may need to stop taking estrogens.

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- 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.

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7. Refer to your health care provider or pharmacist for guidance, and for additional information contact the Coalition for Safe Community Needle Disposal online at http://www.safeneedledisposal.org or refer to the FDA website Needles and Other Sharps at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/Sharps/default.htm

How should I dispose of expired or unused Estradiol Valerate Injection?

1. Do not flush unused Estradiol Valerate Injection or pour down the sink or drain.
2. Refer to the state or local laws and regulations for the safest and proper disposal of injectable medications. Contact your city or county government's household trash and recycling service to find out if a drug take-back program is available in your community. You can also refer to your health care provider or pharmacist for guidance.
3. For additional information refer to the following FDA websites:

   Disposal of Unused Medicines: What You Should Know

   http://www.fda.gov/drugs/resourcesforyou/consumers/buyngusingmedicinesafely/ensureings afeuseofmedicine/safedisposalofmedicines /ucm186187.htm
   How to Dispose of Unused Medicines
   http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/Understandingover-the-CounterMedicines/ucm107163.pdf

What are the possible side effects of estrogens?

Less common but serious side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

Common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus ("fibroids")
- Vaginal yeast infection

These are not all the possible side effects of Estradiol Valerate Injection. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of a serious side effect with Estradiol Valerate Injection?
Talk with your healthcare provider regularly about whether you should continue taking Estradiol Valerate Injection. If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you. See your healthcare provider right away if you get vaginal bleeding while taking Estradiol Valerate Injection. Have a breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often. If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease.

General information about safe and effective use of Estradiol Valerate Injection
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take Estradiol Valerate Injection for conditions for which it was not prescribed. Do not give Estradiol Valerate Injection to other people, even if they have the same symptoms you have. It may harm them.

Keep Estradiol Valerate Injection out of the reach of children
This leaflet provides a summary of the most important information about Estradiol Valerate Injection. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Estradiol Valerate Injection that is written for health professionals. You can get more information by calling the toll free number 1-866-634-9120.

What are the ingredients in Estradiol Valerate Injection?
Estradiol Valerate Injection is supplied in two 5 mL multiple dose vials; 20 mg/mL and 40 mg/mL strengths. The 20 mg/mL strength contains 20 mg estradiol valerate in a solution of benzyl benzoate, benzyl alcohol, and castor oil. The 40 mg/mL strength contains 40 mg estradiol valerate in a solution of benzyl benzoate, benzyl alcohol, and castor oil.

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Store Estradiol Valerate Injection at room temperature between 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.)

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

American Regent, Inc.
Shirley, NY 11967

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Rev. 11/19

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Store Estradiol Valerate Injection at room temperature between 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.)

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

American Regent, Inc.
Shirley, NY 11967

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7. Refer to your health care provider or pharmacist for guidance, and for additional information contact the Coalition for Safe Community Needle Disposal online at http://www.safeneedledisposal.org or refer to the FDA website Needles and Other Sharps at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/Sharps/default.htm

How should I dispose of expired or unused Estradiol Valerate Injection?

1. Do not flush unused Estradiol Valerate Injection or pour down the sink or drain.
2. Refer to the state or local laws and regulations for the safest and proper disposal of injectable medications. Contact your city or county government's household trash and recycling service to find out if a drug take-back program is available in your community. You can also refer to your health care provider or pharmacist for guidance.
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   Disposal of Unused Medicines: What You Should Know

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What are the possible side effects of estrogens?

Less common but serious side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

Common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus ("fibroids")
- Vaginal yeast infection

These are not all the possible side effects of Estradiol Valerate Injection. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of a serious side effect with Estradiol Valerate Injection?
Talk with your healthcare provider regularly about whether you should continue taking Estradiol Valerate Injection. If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you. See your healthcare provider right away if you get vaginal bleeding while taking Estradiol Valerate Injection. Have a breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often. If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease.

General information about safe and effective use of Estradiol Valerate Injection
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take Estradiol Valerate Injection for conditions for which it was not prescribed. Do not give Estradiol Valerate Injection to other people, even if they have the same symptoms you have. It may harm them.

Keep Estradiol Valerate Injection out of the reach of children
This leaflet provides a summary of the most important information about Estradiol Valerate Injection. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Estradiol Valerate Injection that is written for health professionals. You can get more information by calling the toll free number 1-866-634-9120.

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

8. ***Exacerbation of endometriosis***
   Endometriosis may be exacerbated with administration of estrogens. A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

9. ***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.

10. ***Hypercoagulability***
    Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have increased coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low dose postmenopausal mestranol may increase the risk of thromboembolism, although the majority of studies (of primarily conjugated estrogens users) report no such increase.

11. ***Uterine bleeding and mastodynia***
    Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.

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

C. 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 (e.g., estradiol, FSH).

D. Drug/Laboratory Test Interactions

1. 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.
2. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), sex hormone binding globulin (SHBG)) 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).
4. Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentrations, increased triglycerides levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.

E. 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. (See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS**.)

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

F. Pregnancy
Estradiol Valerate Injection should not be used during pregnancy. (See **CONTRAINDICATIONS**.)

G. 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.

H. 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. Therefore, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended in patients in whom bone growth is not complete.

I. Geriatric Use
Clinical studies of estradiol valerate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of 4 years, 82% (n = 3,729) were 65 to 74 while 18% (n = 803) were 75 and over. Most women (80%) had no prior hormone therapy 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 of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of the women that were older than 70. (See **WARNINGS, Dementia**.)

It is unknown whether these findings apply to estrogen alone therapy.

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 adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

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

1. **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.
2. **Breasts**
   Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.
3. **Cardiovascular**
   Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.
4. **Gastrointestinal**
   Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis, enlargement of hepatic hemangiomas.
5. **Skin**
   Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.
6. **Eyes**
   Retinal vascular thrombosis; intolerance to contact lenses.
7. **Central Nervous System**
   Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy, dementia.
8. **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 medical advice about adverse reactions contact your medical professional. To report SUSPECTED ADVERSE REACTIONS, contact American Regent, Inc. at 1-800-734-9236 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing drug products by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

When estrogen is prescribed for a postmenopausal woman with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (e.g., 3-month to 6-month intervals) to determine if treatment is still necessary. (See **BOXED WARNINGS** and **WARNINGS.**) For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Care should be taken to inject deeply into the upper, outer quadrant of the gluteal muscle following the usual precautions for intramuscular administration. By virtue of the low viscosity of the vehicles, the various preparations of Estradiol Valerate Injection may be administered with a small gauge needle (i.e., 20 Gauge x 1 1/2 inches long). Since the 40 mg potency provides a high concentration in a small volume, particular care should be observed to administer the full dose.

Estradiol Valerate Injection should be visually inspected for particulate matter and color prior to administration; the solution is clear, colorless to yellow. Storage at low temperatures may result in the separation of some crystalline material which redissolves readily on warming.

Note: A dry needle and syringe should be used. Use of a wet needle or syringe may cause the solution to become cloudy; however, this does not affect the potency of the material.

Patients should be started at the lowest dose for the indication. The lowest effective dose of Estradiol Valerate Injection has not been determined for any indication. Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer, and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding. See **PRECAUTIONS** concerning addition of a progestin.

1. **For treatment of moderate to severe vasomotor symptoms, vulvar and vaginal atrophy associated with the menopause, the lowest dose and regimen that will control symptoms should be chosen and medication should be discontinued as promptly as possible.**
   The usual dosage is 10 to 20 mg Estradiol Valerate Injection, USP every four weeks.
   Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals.
2. **For treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.**
   The usual dosage is 10 to 20 mg Estradiol Valerate Injection, USP every four weeks.
3. **For treatment of advanced androgen-dependent carcinoma of the prostate, for palliation only.**
   The usual dosage is 30 mg or more administered every one or two weeks.

HOW SUPPLIED

Estradiol Valerate Injection, USP
Multiple Dose Vials

NDC 0517-0420-01	20 mg/mL (5 mL)
NDC 0517-0440-01	40 mg/mL (5 mL)

STORAGE

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Keep out of reach of children.

PROTECT FROM LIGHT. Store vial in carton until used.

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.

What is Estradiol Valerate Injection?
Estradiol Valerate Injection is a medicine that contains estrogen hormones.

What is Estradiol Valerate Injection used for?
Estradiol Valerate Injection is used after menopause to:

- **reduce moderate to severe hot flashes.** Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 to 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."

  When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feeling of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women, the symptoms are mild, and they will not need estrogens. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether you still need treatment with Estradiol Valerate Injection.
- **treat moderate to severe dryness, itching, and burning in and around the vagina.** You and your healthcare provider should talk regularly about whether you still need treatment with Estradiol Valerate Injection to control these problems. If you use Estradiol Valerate Injection only to treat your dryness, itching, and burning in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.

Who should not take Estradiol Valerate Injection?
Do not start taking Estradiol Valerate Injection if you:

- **have unusual vaginal bleeding.**
- **currently have or have had certain cancers.** Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or had cancer, talk with your healthcare provider about whether you should take Estradiol Valerate Injection.
- **had a stroke or heart attack in the past year.**
- **currently have or have had blood clots.**
- **currently have or have had liver problems.**
- **are allergic to Estradiol Valerate Injection or any of its ingredients.** See the end of this leaflet for a list of ingredients in Estradiol Valerate Injection.
- **think you may be pregnant.**

Tell your healthcare provider:

- **if you are breastfeeding.** The hormone in Estradiol Valerate Injection can pass into your milk.
- **about all of your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **about all the medicines you take.** This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Estradiol Valerate Injection works. Estradiol Valerate Injection may also affect how your other medicines work.
- **if you are going to have surgery or will be on bed rest.** You may need to stop taking estrogens.

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Note: A dry needle and syringe should be used. Use of a wet needle or syringe may cause the solution to become cloudy; however, this does not affect the potency of the material.

1. Start at the lowest dose and talk to your healthcare provider about how well that dose is working for you.
2. Estrogens should be used at the lowest dose possible for your treatment only as long as needed. The lowest effective dose of Estradiol Valerate Injection has not been determined. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with Estradiol Valerate Injection.

How should I dispose of used syringes and needles?

1. Do not re-use needles or syringes.
2. Do not throw the needles and syringes in household waste. These should be discarded into an appropriate container (such as a sharps container) immediately after use. Refer to state or local laws and regulations for appropriate container requirements.
3. Make sure the container is tightly capped.
4. Strategically place the container so as to minimize handling and keep out of the reach of children.
5. Label the container indicating the presence of used needles/sharps.
6. For disposal of containers containing used needles and syringes refer to the state or local laws and regulations or as instructed by your healthcare provider or pharmacist.
7. Refer to your health care provider or pharmacist for guidance, and for additional information contact the Coalition for Safe Community Needle Disposal online at http://www.safeneedledisposal.org or refer to the FDA website Needles and Other Sharps at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/Sharps/default.htm

How should I dispose of expired or unused Estradiol Valerate Injection?

1. Do not flush unused Estradiol Valerate Injection or pour down the sink or drain.
2. Refer to the state or local laws and regulations for the safest and proper disposal of injectable medications. Contact your city or county government's household trash and recycling service to find out if a drug take-back program is available in your community. You can also refer to your health care provider or pharmacist for guidance.
3. For additional information refer to the following FDA websites:

Disposal of Unused Medicines: What You Should Know

http://www.fda.gov/drugs/resourcesforyou/consumers/buyngusingmedicinesafely/ensureings afeuseofmedicine/safedisposalofmedicines/ucm186187.htm
How to Dispose of Unused Medicines
http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/Understandingover-the-CounterMedicines/ucm107163.pdf

What are the possible side effects of estrogens?

Less common but serious side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

Common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus ("fibroids")
- Vaginal yeast infection

These are not all the possible side effects of Estradiol Valerate Injection. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of a serious side effect with Estradiol Valerate Injection?
Talk with your healthcare provider regularly about whether you should continue taking Estradiol Valerate Injection. If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you. See your healthcare provider right away if you get vaginal bleeding while taking Estradiol Valerate Injection. Have a breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often. If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease.

General information about safe and effective use of Estradiol Valerate Injection
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take Estradiol Valerate Injection for conditions for which it was not prescribed. Do not give Estradiol Valerate Injection to other people, even if they have the same symptoms you have. It may harm them.

Keep Estradiol Valerate Injection out of the reach of children
This leaflet provides a summary of the most important information about Estradiol Valerate Injection. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Estradiol Valerate Injection that is written for health professionals. You can get more information by calling the toll free number 1-866-634-9120.

What are the ingredients in Estradiol Valerate Injection?
Estradiol Valerate Injection is supplied in two 5 mL multiple dose vials; 20 mg/mL and 40 mg/mL strengths. The 20 mg/mL strength contains 20 mg estradiol valerate in a solution of benzyl benzoate, benzyl alcohol, and castor oil. The 40 mg/mL strength contains 40 mg estradiol valerate in a solution of benzyl benzoate, benzyl alcohol, and castor oil.

How should I store Estradiol Valerate Injection?
Store Estradiol Valerate Injection at room temperature between 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.)

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

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RQ1090-A
Rev. 11/19