

## **DELESTROGEN<sup>®</sup>**

(ESTRADIOL VALERATE INJECTION, USP)

### **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 with and without 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 during 5 years of treatment with conjugated equine estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo (see **CLINICAL PHARMACOLOGY, Clinical Studies**). Other doses of conjugated estrogens with medroxyprogesterone, and other combinations of estrogens and progestins were not studied in the WHI 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.

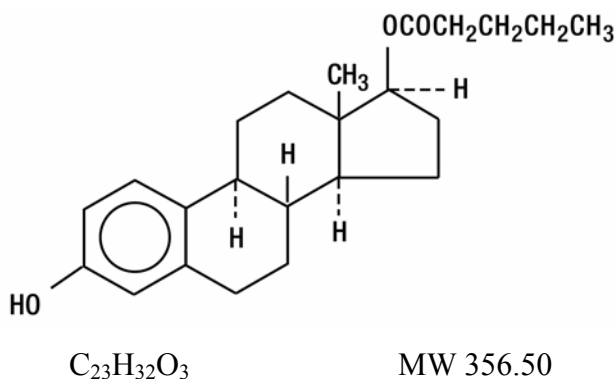
## **DESCRIPTION**

DELESTROGEN<sup>®</sup> (estradiol valerate injection, USP) contains estradiol valerate, a long-acting estrogen in sterile oil solutions for intramuscular use. These solutions are clear, colorless to pale yellow. Formulations (per mL): 10 mg estradiol valerate in a vehicle containing 5 mg chlorobutanol (chloral derivative/preservative) and sesame oil; 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 $\beta$ )-, 17-pentanoate.

Graphic formula:



## CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is 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 micrograms 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.

### *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 0.625 mg conjugated equine estrogens (CE) per day alone or the use of 0.625 mg conjugated equine 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-only substudy is continuing and results have not been reported. 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:

Event <sup>c</sup>	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
<i>Non-fatal MI</i>	<i>1.32 (1.02-1.72)</i>	23	30
<i>CHD death</i>	<i>1.18 (0.70-1.97)</i>	6	7
Invasive breast cancer <sup>b</sup>	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 <sup>c</sup>	1.15 (1.03-1.28)	151	170
Deep vein thrombosis <sup>d</sup>	2.07 (1.49-2.87)	13	26
Vertebral fractures <sup>d</sup>	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures <sup>d</sup>	0.77 (0.69-0.86)	170	131

<sup>a</sup>adapted from JAMA, 2002; 288:321-333

<sup>b</sup>includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer

<sup>c</sup>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

<sup>d</sup>not included in Global Index

<sup>\*</sup>nominal confidence intervals unadjusted for multiple looks and multiple comparisons

For those outcomes included in the “global index,” absolute excess risks per 10,000 person-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 person-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 person-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNING, WARNINGS, and PRECAUTIONS.**)

## **INDICATIONS AND USAGE**

DELESTROGEN (estradiol valerate injection, USP) is indicated in the:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulval 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).

## **CONTRAINDICATIONS**

Estrogens should not be used in individuals with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of cancer of the breast except in appropriately selected patients being treated for metastatic disease.
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. DELESTROGEN should not be used in patients with known hypersensitivity to its ingredients.
7. Known or suspected pregnancy. There is no indication for DELESTROGEN in pregnancy. There appears to be little or no increased risk of birth defects in 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 have 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 cardiovascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) should be managed appropriately.

#### **a. *Coronary heart disease and stroke***

In the Women's Health Initiative study (WHI), an increase in the number of myocardial infarctions and strokes has been observed in women receiving CE compared to placebo. These observations are preliminary, and the study is continuing. (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 person 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 person-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 study (WHI), an increase in VTE has been observed in women receiving CE compared to placebo. These observations are preliminary, and the study is continuing. (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 woman-years in the CE/MPA group compared to 16 per 10,000 woman-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***

Estrogen and estrogen/progestin therapy in postmenopausal women has been associated with an increased risk of breast cancer. In the CE/MPA substudy of the Women's Health Initiative study (WHI), a 26% increase of invasive breast cancer (38 vs 30 per 10,000 woman-years) after an average of 5.2 years of treatment was observed in women receiving CE/MPA compared to women receiving placebo. The increased risk of breast cancer became apparent after 4 years on CE/MPA. The women reporting prior postmenopausal use of estrogens and/or estrogen with progestin had a higher relative risk for breast cancer associated with CE/MPA than those who had never used these hormones. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

In the WHI, no increased risk of breast cancer in CE-treated women compared to placebo was reported after an average of 5.2 years of therapy. These data are preliminary and that substudy of WHI is continuing.

Epidemiologic studies have reported an increased risk of breast cancer in association with increasing duration of postmenopausal treatment with estrogens with or without progestin. This association was reanalyzed in original data from 51 studies that involved various doses and types of estrogens, with and without progestins. In the reanalysis, an increased risk of having breast cancer diagnosed became apparent after about 5 years of continued treatment, and subsided after treatment had been discontinued for 5 years or longer. Some later studies have suggested that postmenopausal treatment with estrogens and progestin increase the risk of breast cancer more than treatment with estrogen alone.

A postmenopausal woman without a uterus who requires estrogen should receive estrogen-alone therapy, and should not be exposed unnecessarily to progestins. All postmenopausal women should receive yearly breast exams by a health care provider and perform monthly self-examinations. In addition, mammography examinations should be scheduled based on patient age and risk factors.

**3. Gallbladder disease**

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

**4. 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.

## **5. 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 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. A possible increased risk of breast cancer
- b. Adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL)
- c. Impairment of glucose tolerance

#### **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. Familial hyperlipoproteinemia**

In patients with familial defects of lipoprotein metabolism, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

#### **4. Impaired liver function**

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<sub>4</sub> and T<sub>3</sub> 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.

### **7. Hypocalcemia**

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

### **8. Ovarian cancer**

Use of estrogen-only products, in particular for ten or more years, has been associated with an increased risk of ovarian cancer in some epidemiological studies. Other studies did not show a significant association. Data are insufficient to determine whether there is an increased risk with estrogen/progestin combination therapy in postmenopausal women.

### **9. Exacerbation of endometriosis**

Endometriosis may be exacerbated with administration of estrogens.

### **10. Exacerbation of other conditions**

Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria and should be used with caution in women with these conditions.

### **11. 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.

## **12. 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 DELESTROGEN.

### **C. Laboratory Tests**

Estrogen administration should be initiated at the lowest dose for the approved 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<sub>4</sub> levels (by column or by radioimmunoassay) or T<sub>3</sub> levels by radioimmunoassay. T<sub>3</sub> resin uptake is decreased, reflecting the elevated TBG. Free T<sub>4</sub> and free T<sub>3</sub> 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 circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL<sub>2</sub> subfraction concentrations, reduced LDL cholesterol concentration, 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 natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. (See **BOXED WARNINGS, CONTRAINDICATIONS, and WARNINGS.**)

#### **F. Pregnancy**

Estrogens 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 DELESTROGEN 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.

### **ADVERSE REACTIONS**

See **BOXED WARNINGS, WARNINGS, and PRECAUTIONS.**

The following additional adverse reactions have been reported with estrogens:

#### **1. Genitourinary system**

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; 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.

## **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; steepening of corneal curvature; intolerance to contact lenses.

## **7. Central Nervous System**

Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy.

## **8. Miscellaneous**

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

## **OVERDOSAGE**

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing oral contraceptives 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 limited to 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 DELESTROGEN (estradiol valerate injection, USP) may be administered with a small gauge needle. Since the 40 mg potency provides a high concentration in a small volume, particular care should be observed to administer the full dose.

DELESTROGEN should be visually inspected for particulate matter and color prior to administration; the solution is clear, colorless to pale 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 effective dose for the indication.**

- 1. For treatment of moderate to severe vasomotor symptoms, vulval 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.**

Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals. The usual dosage is 10 to 20 mg DELESTROGEN every four weeks.

- 2. For treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.**

The usual dosage is 10 to 20 mg DELESTROGEN 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.

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 A.1** concerning addition of a progestin.

## **HOW SUPPLIED**

DELESTROGEN<sup>®</sup> (estradiol valerate injection, USP)

### *Multiple Dose Vials*

10 mg/mL (5 mL): NDC 61570-180-01

20 mg/mL (5 mL): NDC 61570-181-01

40 mg/mL (5 mL): NDC 61570-182-01

## **Storage**

Store at room temperature.

## **PATIENT INFORMATION**

(Updated December 2, 2003)

### **DELESTROGEN<sup>®</sup>** **(estradiol valerate injection, USP)**

Read this **PATIENT INFORMATION** before you start taking DELESTROGEN and read what you get each time you refill DELESTROGEN. There may be new information. This information does not take the place of talking to your health care provider about your medical condition or your treatment.

#### **What is the most important information I should know about DELESTROGEN (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 health care 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 attack, strokes, breast cancer, and blood clots. You and your health care provider should talk regularly about whether you still need treatment with DELESTROGEN.

#### **What is DELESTROGEN?**

DELESTROGEN is a medicine that contains estrogen hormones.

#### **What is DELESTROGEN used for?**

DELESTROGEN 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 in 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 health care provider should talk regularly about whether you still need treatment with DELESTROGEN.

- **treat moderate to severe dryness, itching, and burning in or around the vagina.** You and your health care provider should talk regularly about whether you still need treatment with DELESTROGEN to control these problems.
- **help reduce your chances of getting osteoporosis (thin weak bones).** Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use DELESTROGEN only to prevent osteoporosis from menopause, talk with your health care provider about whether a different treatment or medicine without estrogens might be better for you. You and your health care provider should talk regularly about whether you should continue with DELESTROGEN.

Weight-bearing exercise, like walking or running, and taking calcium and vitamin D supplements may also lower your chances of getting postmenopausal osteoporosis. It is important to talk about exercise and supplements with your health care provider before starting them.

### **Who should not take DELESTROGEN?**

Do not start taking DELESTROGEN 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 health care provider about whether you should take DELESTROGEN.
- **had a stroke or heart attack in the past year.**
- **currently have or have had blood clots.**
- **are allergic to DELESTROGEN or any of its ingredients.** See the end of this leaflet for a list of ingredients in DELESTROGEN.

- **think you may be pregnant.**

**Tell your health care provider:**

- **if you are breastfeeding.** The hormone in DELESTROGEN can pass into your milk.
- **about all of your medical problems.** Your health care provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **about all the medicines you take,** including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how DELESTROGEN works. DELESTROGEN 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 DELESTROGEN?**

DELESTROGEN 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 DELESTROGEN (estradiol valerate injection, USP) may be administered with a small gauge needle. Since the 40 mg potency provides a high concentration in a small volume, particular care should be observed to administer the full dose.

DELESTROGEN should be visually inspected for particulate matter and color prior to administration; the solution is clear, colorless to pale 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.

Estrogens should be used only as long as needed. You and your health care provider should talk regularly (for example, every 3 to 6 months) about whether you still need treatment with DELESTROGEN.

**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
- 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 health care 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 DELESTROGEN. For more information, ask your health care provider or pharmacist.

**What can I do to lower my chances of a serious side effect with DELESTROGEN?**

- Talk with your health care provider regularly about whether you should continue taking DELESTROGEN.
- See your health care provider right away if you get vaginal bleeding while taking DELESTROGEN.

- Have a breast exam and mammogram (breast X-ray) every year unless your health care 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 health care provider for ways to lower your chances for getting heart disease.

### **General information about safe and effective use of DELESTROGEN**

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take DELESTROGEN for conditions for which it was not prescribed. Do not give DELESTROGEN to other people, even if they have the same symptoms you have. It may harm them.

### **Keep DELESTROGEN out of the reach of children.**

This leaflet provides a summary of the most important information about DELESTROGEN. If you would like more information, talk with your health care provider or pharmacist. You can ask for information about DELESTROGEN that is written for health professionals. You can get more information by calling the toll free number 1-800-776-3637, select option 5.

### **What are the ingredients in DELESTROGEN?**

DELESTROGEN is supplied in three 5 mL multiple dose vials; 10 mg/mL, 20 mg/mL, and 40 mg/mL strengths. The 10 mg/mL strength contains 10 mg estradiol valerate in a solution of chlorobutanol and sesame oil. 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.



Distributed by: Monarch Pharmaceuticals, Inc., Bristol, TN 37620

(A wholly owned subsidiary of King Pharmaceuticals, Inc.)

Manufactured by: Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

Prescribing Information as of December 2, 2003.

